Toxoplasmosis-Associated Neovascular Lesions Treated Successfully With Ranibizumab and Antiparasitic Therapy

Choroidal neovascular membranes (CNVMs) rarely complicate toxoplasmic chorioretinitis and are managed by observation; antiparasitic, anti-inflammatory medication; laser photocoagulation; surgical excision; or photodynamic therapy, with variable outcomes. As occurs with CNVMs secondary to age-related macular degeneration, Toxoplasma gondii increases expression of hypoxia-inducible factor–α in tissue cultures along with vascular endothelial growth factor (VEGF).

Report of Cases. Two patients with prior ocular toxoplasmosis had active CNVMs with subretinal blood and fluid on clinical examination and ocular coherence tomography (OCT) and hyperfluorescence with leakage documented on fluorescein angiogram (FA). Each was treated with off-label intravitreal injections of ranibizumab (Genentech, Inc, South San Francisco, California) and antiparasitic treatment, with responses documented with measurements of visual acuity, full fundus photographs, FA, and OCT. We reviewed courses and photographs of 187 persons with toxoplasmosis, 175 definitely congenitally acquired, followed up in the National Collaborative Chicago-based Congenital Toxoplasmosis Study to identify those who had recognized ocular neovascular disease. Three persons had a CNVM and 1 had a retinal angioma with exudation.

Institutional review board approval was obtained for this study. Written informed consent was obtained from parents or legal guardians of participating children and directly from patients (if legal adult age). This study is in compliance with Health Insurance Portability and Accountability Act of 1996 regulations.

Unless otherwise specified, reported visual acuities are best-corrected visual acuity.

Case 1. A 25-year-old man was seen with a complaint of abrupt onset of decreased vision of the left eye for 1 week. He reported that he could not distinguish faces, see television, distinguish numbers on the face of a clock or on the dashboard of his car or fingers held up in an examination room, or distinguish the lines on an Amsler grid. He had a history of decreased vision in the right eye since age 12 years secondary to a macular scar attributed to ocular toxoplasmosis, and he said that in the prior week his vision in his left eye had become as severely impaired as the vision in his right eye. Results of a Toxoplasma dye test with undiluted serum in the US reference laboratory were positive and serology results were negative for antibody to Histoplasma. A brain computed tomographic scan showed no abnormalities. His visual acuity at the initial visit was 20/400 OD and 20/50 OS; his visual acuity had been 20/20 OS. Results of tonometry and anterior segment examination were within normal limits in each eye. There was no anterior chamber inflammation or vitritis in either eye.

Fundus examination of the right eye revealed an inactive macular chorioretinal scar along with peripapillary and peripheral scars. The left fundus similarly showed peripapillary and peripheral chorioretinal scars. There was subretinal fluid with retinal striae, and subretinal hemorrhage was evident within the macula tracking toward the fovea. An FA and OCT demonstrated a peripapillary CNVM with hemorrhage.

After extensive discussions and consideration of all options, we and the patient decided to perform an off-label intravitreal injection of 0.5 mg of ranibizumab in the left eye with concurrent systemic administration of oral pyrimethamine, sulfadiazine, and leukovorin. One month following initial injection and initiation of medical treatment, visual acuity improved to 20/20 OS. There was resolution of a significant portion of the subretinal hemorrhage and subretinal fluid, and degree of hyperfluorescence of the CNVM had decreased.

One more ranibizumab treatment was administered at this visit. One month later there was a small amount of residual subretinal hemorrhage without leakage of fluorescein or pres-
ence of subretinal fluid noted clinically or with OCT (Figure 1). Complete involution of the CNVM, resolution of the subretinal fluid and hemorrhage, and maintenance of 20/20 acuity were documented by the second month after treatment. Visual acuity remained between 20/20 and 20/15, and examination documented that the CNVM was no longer present 6 months after the initial ranibizumab injection (Figure 1). Clearing subretinal hemorrhage revealed a lesion superior to the optic disc with initially soft blurred edges and eventually sharply demarcated edges with pigment around the perimeter (Figure 1). Anti-Toxoplasma medicines were continued until 2 weeks after the edges of the scar became sharply demarcated and pigmented.

Case 2. A 7-year-old boy had a CNVM with hemorrhage 1 month prior to his initial visit with us for this problem. At this visit with us, he described complete loss of vision and had a visual acuity of hand motion OD. He was treated 1 year prior to this examination for active toxoplasmic chorioretinitis and had a right macular chorioretinal scar. He had a visual acuity of 20/40 OD following treatment of the acute episode and visual acuity of 20/20 OS. He had progressive visual loss in the right eye during the subsequent year. He had undergone unilateral strabismus surgery in the right eye for esotropia, with perioperative use of topical steroids without antiparasitic treatment 5 months prior to his initial visit with us for this problem. He reported gradual worsening of vision and, by the week prior to his initial visit with us for this problem, he reported that he could not see with this eye at all. Results of tonometry and anterior segment examination were within normal limits in each eye. There was no aqueous or vitreous inflammation in either eye. Subretinal hemorrhage surrounded a macular scar in the right eye (Figure 2). There was leakage recorded by FA. Optical coherence tomography revealed cystic spaces overlying the area of increased transmission through the atrophic lesion, with the CNVM adjacent to this area elevating the overlying retina (Figure 2).

When initially diagnosed at 6 years of age, his Sabin-Feldman dye test result was 1:2048 in the US reference laboratory and his mother's serology results were negative for T gondii. He had no IgM, IgA, or IgE antibodies to T gondii and his differential agglutination (AC/HS) test indicated a chronic infection. A brain computed tomographic scan showed no abnormalities.

After careful consideration by his parents and all physicians caring for the child, off-label intravitreal injection of 0.5 mg of ranibizumab was performed with concurrent oral administration of pyrimethamine, sulfadiazine, and leukovorin. This intravitreal ranibizumab treatment was repeated 4 weeks and 8 weeks after the initial treatment. Because of transient neutropenia during the prodrome of a viral infection, this treatment was changed to a lower dose of pyrimethamine and clarithromycin. Sulfadiazine administration was discontinued. Neutropenia resolved and neither neutropenia nor any other problems were noted at any other time during treatment, including with the subsequent ranibizumab injections. The child was followed up with fundus photographs every 1 to 2 weeks throughout treatment.

Seven weeks after the first ranibizumab injection, fundus photographs and FA showed complete resolution of much of the subretinal hemorrhage with a concurrent decrease in the size of the CNVM. Optical coherence tomography documented resorption of cystic fluid and flattening of the CNVM. Eleven weeks after the first ranibizumab injection, fundus photographs and FA showed complete resolution of the subretinal hemorrhage and involution of the CNVM. There was a small amount of cystic fluid accumulation on OCT. Visual acuity improved to 20/100 at distance and 20/40 at near 11 weeks after the initial ranibizumab injection. Treatment was continued for 3 injections and he currently is being followed up. Antiparasitic medications were continued throughout, and 1 week after the last ranibizumab injection, pyrimethamine administration was discontinued followed by an additional week of leukovorin treatment. Clarithromycin administration alone has been continued.

Comment. Increased expression of VEGF, in addition to compromise in the Bruch membrane and inflammation secondary to infection with T gondii, may contribute to neovascular disease in ocular toxoplasmosis. Increased expression of hypoxia-inducible factor–1α and VEGF...
caused by *T gondii* in tissue culture provides a rationale for specifically targeting VEGF to treat CNVMs in ocular toxoplasmosis.

Six patients with ocular toxoplasmosis and neovascular disease (Table, Figures 1, 2, and 3) were diagnosed with ocular toxoplasmosis when younger than 12 years. Neovascularization developed between ages 4 and 25 years. None had been treated with antiparasitic medicines in utero or their first year of life. Two patients were treated with anti-VEGF therapy and anti-Toxoplasma medicines; 1, with photodynamic therapy only; and 2, with only antiparasitic medicines (Figure 4). One patient with acquired retinal angioma, exudate, and partial serous retinal detachment was treated with anti-VEGF and antiparasitic medicines. She developed a progressive subretinal exudate with frank macular detachment and a drop in visual acuity to 2400. She had a scleral buckle and vitrectomy procedure on the left eye with peeling of posterior membranes, cryopexy to the vasoproliferative lesion, and laser barricade posterior to the buckle. The buckle was placed high and over the areas of significant traction and vasoproliferation. An air-fluid exchange was performed. Antiparasitic medicines were continued until the process resolved. This restored visual acuity to 20/60 at present and there appears to be continuing improvement in visual acuity.

Questions remain about how and when to treat these vascular lesions in ocular toxoplasmosis. Anti-VEGF therapy has potential to provide a more favorable visual outcome than other therapies since it minimizes destruction of the retina and choroid, especially for subfoveal or juxtafoveal CNVM or lesions with edges obscured by subretinal hemorrhage. Because active infectious retinitis may be obscured by hemorrhage or be difficult or impossible to distinguish from CNVM and because injections may reactivate chorioretinitis, concurrent therapy with oral anti-Toxoplasma medicine and ranibizumab was prescribed for our 2 patients (Table) (Figure 4). The characteristic pattern of resolution of the lesion with visualization of a scar with indistinct borders as hemorrhage first resolved and then healing with well-demarcated pigmentation in patient 1 is consistent with the typical pattern of resolution of active toxoplasmo-

### Table. Brief Description of Children With Ocular Toxoplasmosis and CNVMa

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Time Neovascular Lesion Noted, y</th>
<th>Lesion Type</th>
<th>Probable Duration of Lesionb</th>
<th>Antiparasitic Treatmentc</th>
<th>Treatment of Neovascular Lesion (No. of Injections)</th>
<th>Prelesion Visual Acuity</th>
<th>Visual Acuity at Time of Treatment</th>
<th>Posttreatment Visual Acuityd</th>
<th>Time to Resolution/Duration of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>CNVM</td>
<td>1 wk</td>
<td>Yes</td>
<td>Ranibizumab (2)</td>
<td>20/20</td>
<td>20/50</td>
<td>20/20</td>
<td>2 mo/1 y 3 mo</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>CNVM</td>
<td>&gt;1 mo</td>
<td>Yes</td>
<td>Ranibizumab (3)</td>
<td>20/40</td>
<td>20/100</td>
<td>20/20</td>
<td>11 wk/1 y</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>CNVM</td>
<td>&lt;1 y</td>
<td>No</td>
<td>PDT</td>
<td>20/40</td>
<td>20/60</td>
<td>20/60</td>
<td>Ongoing/6 y</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>CNVM</td>
<td>&lt;1 y</td>
<td>Yes</td>
<td>None</td>
<td>20/30</td>
<td>20/30</td>
<td>20/25</td>
<td>NA/13 y</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>CNVM</td>
<td>&gt;2 y</td>
<td>Yes</td>
<td>Ranibizumab</td>
<td>20/30</td>
<td>20/40</td>
<td>NA</td>
<td>In progress</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>Angioma</td>
<td>&gt;6 mo</td>
<td>Yes</td>
<td>None</td>
<td>20/60</td>
<td>20/60</td>
<td>20/50</td>
<td>1 y/15 y</td>
</tr>
</tbody>
</table>

Abbreviations: CNVM, choroidal neovascular membrane; HM, hand motions; NA, data not available; PDT, photodynamic therapy.

a Also see Figure 4.

b The duration of symptoms noted by the patient suggested the presence of neovascular lesions. Actual duration is especially imprecise in younger patients who may not have perceived or complained of any symptoms. In these cases, the durations are given as an interval greater than the time between the lesion’s first appearance on clinical examination and the date of treatment or an interval less than the time between the date of the last normal examination and the first time the lesion was noted on clinical examination.

c Antiparasitic treatment was given before, throughout, and at least 1 week after treatment with anti-vascular endothelial growth factor. Treatment started with pyrimethamine, sulfadiazine, and leukovorin and then after 6 weeks in some instances clindamycin was substituted for sulfadiazine. Leukovorin was administered throughout and for 1 week after the time pyrimethamine was administered. Treatment with these medicines was continued for about 1 month beyond resolution of the CNVM and at least 1 week after activity of toxoplasmic retinitis.

d Visual acuity is best-approximated visual acuity unless otherwise stated in the text. These measurements do not reflect defects in visual field that also impaired vision and were larger with larger scars. In some instances, these defects were the major morbidity of the lesions and their treatment (eg, with PDT). In prior reports, surgical excision in 2 patients and PDT in 4 small series have been reported as treatments for CNVM in ocular toxoplasmosis. With surgical excision, 2 patients improved to 20/20 and 20/30. With PDT, for 14 reported patients, 3 patients worsened, 5 had partial improvement in vision but not to baseline, 1 improved to baseline, and 5 stabilized or improved with treatment but baseline visions were not provided. Cryotherapy or endophotocoagulation resulted in resorption of exudative fluid in 5 of 7 eyes with angiomatic lesions associated with *Toxoplasma* scars. In many instances, defects in visual field were the major morbidity of the lesions and their treatment with PDT and were not quantified or mentioned.

Figure 3. Fundus photographs of patients 3, 4, 5, and 6. Patient 3 before choroidal neovascular membrane (CNVM) (top row) and 4 years after photodynamic therapy (bottom row). Patient 4 with CNVM (top row) and 3 months later (bottom row). Patient 5 with CNVM (top row) and 4 years later (bottom row). Patient 6 before (top row) and after development of angiomatic proliferation (bottom row).
mic chorioretinitis with medical treatment. The lesion did not appear to be toxoplasmic chorioretinitis alone because of extensive subretinal fluid and subretinal hemorrhage. Choroidal neovascular membranes also occur in other ocular infections (eg, histoplasmosis), suggesting a similar pathogenesis.

Safety of anti-VEGF therapy in infants, children, and young adults and its longer-term efficacy remain to be established. It appears to have been well-tolerated in our patients and in infants described by Capone. Favorable outcome in our 2 patients indicates that intravitreal ranibizumab therapy plus anti–T gondii medicines have potential to be efficacious in treatment of ocular neovascularization secondary to ocular toxoplasmosis.

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Small Choroidal Melanomas Treated With Transpupillary Thermotherapy and Cryotherapy

The management of small choroidal melanomas continues to be controversial. Although radiotherapy with either charged particles or ionizing radiation can be effective in providing local control of these tumors, radiation complications (radiation retinopathy and optic neuropathy) that cause loss of vision have led some investigators to consider alternative forms of treatment. One alternative treatment that has been studied by a number of investigators is transpupillary thermotherapy (TTT). Although initial results using TTT to treat selected uveal melanomas were optimistic, a longer follow-up and a relatively high tumor recurrence rate have dampened the initial enthusiasm for TTT as a stand-alone therapy. To minimize the tumor recurrence rate after TTT, adjunctive cryotherapy has been proposed.

The purpose of this report is to review a small cohort of patients who were prospectively treated with a combination of TTT and cryotherapy.

Report of Cases. The institutional review board of the Mayo Medical School approved this study, which was performed in accordance with Health Insurance Portability and Accountability Act regulations. This study is a noncomparative interventional case series. Five patients with small melanomas of the choroid (thickness range, 1.2-2.8 mm) that were located 1.5 mm or more from the optic nerve and the macula underwent TTT. The anterior edge of each tumor was more than 2 disc diameters posterior to the equator. Other criteria for selecting tumors for TTT and the TTT treatment variables have been outlined in a previous publication; all tumors in this series had demonstrated growth or had significant risk factors of growth that included subretinal fluid. Patients who consented to treatment with TTT were advised that their tumors would also be treated with cryotherapy 3 to 4 months after TTT. For the cryotherapy, the surgical site was anesthetized with sub-Tenon lidocaine, and the cryotherapy was delivered under indirect ophthalmoscopic control using a standard retinal cryoprobe. The tip of the probe was then introduced into the sub-Tenon space through a small slit in the conjunctival fornix. In each case, the full tumor thickness was maintained within the freeze for 45 seconds before it was thawed. A subsequent freeze at the same location was given. The probe was then repositioned and additional applications were administered until the entire tumor and a 1-mm perimeter of tumor-free tissue were treated. I delivered all the cryotherapy applications. Follow-up examinations were conducted at 24 to 48 hours, 2 to 6 weeks, and 6-month intervals.

The 5 patients, ranging in age from 35 to 75 years (mean age, 56 years), were treated with combination therapy (TTT and cryotherapy) and followed up from 44 months to 5 years. The tumors ranged in thickness from 1.2 to 2.8 mm. Maximum base dimensions ranged from 6 to 9 mm.

In 2 patients, a recurrence of the tumor was observed despite the combination therapy. One of the patients had lost an eye from trauma. He developed a melanoma in his only eye. A recurrence of the tumor was noted at the edge of the treatment site 40 months after the original combination treatment. This recurrence was treated with additional TTT, and no additional recurrence was found during a further follow-up of 6 months. The tumor recurrence in the other patient was observed 10 months after the original combination treatment. After the TTT but before the cryotherapy, the tumor thickness was reduced from 1.7 mm to less than 0.5 mm. Then, its base was treated with cryotherapy. Seven months after cryotherapy, the tumor was observed to expand in both thickness (1.6 mm) and base dimension (7 mm). The tumor was treated with iodine 125 brachytherapy, and growth of the tumor was arrested. Its thickness remained stable (1.6-1.7 mm), and no further basal expansion of the tumor occurred. However, at the 48-month follow-up, the patient had metastatic melanoma in the liver.

One patient developed a macular epiretinal membrane 1 year after treatment of the melanoma. Despite pars plana vitrectomy and successful membrane peeling, the patient’s visual acuity has remained compromised at 20/80.

Comment. In a recent study by Win et al, tumor recurrences after TTT of small melanomas were observed in 23% of the cases. This recurrence rate was comparable to the Kaplan-Meier 3-year estimated recurrence rate reported in a series of patients with small melanoma treated by Shields et al. These observations, along with the posttreatment occurrence of extrascleral extension in 1 of my patients, led me to begin treating such tumors with transscleral cryotherapy approximately 3 months after TTT. The choice of cryotherapy as an adjunct to TTT was based on the documented success of cryotherapy in destroying small choroidal melanomas when used as a primary treatment. I also used cryotherapy successfully to destroy 1 small-sized melanoma. Because of these observations, I theorized that adjunctive transscleral cryotherapy might minimize the potential for both tumor recurrence and extrascleral extension by destroying mela-