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IS TAMOXIFEN A RISK FACTOR FOR RETINAL VASO-OCCLUSIVE DISEASE?

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# Brief Reports

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## TREATMENT OF GLAUCOMA SECONDARY TO SILICONE OIL RETENTION

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Nineteen eyes with secondary glaucoma due to silicone oil retention after silicone oil removal are described. The mean intraocular pressure  $\pm$  SD was  $37.23 \pm 6.47$  mmHg  $7.89 \pm 2.75$  days after silicone oil removal. In 5 eyes, medical therapy was effective to control intraocular pressure, while the other 14 eyes needed surgery.

Cibis was the first to adopt silicone oil in the treatment of retinal detachment in 1962. With the rapid development of complicated posterior segment surgeries, the use of silicone oil has increased, thus greatly improving the prognosis of proliferative vitreoretinopathy. However, silicone oil-related complications have also appeared. For example, retention of silicone oil after its removal may lead to secondary glaucoma, which is often overlooked and leads to the adverse consequence of delaying treatment. To study clinical features and to evaluate therapeutic efficacy, we reviewed 19 cases (19 eyes) of secondary glaucoma due to silicone oil retention after silicone oil removal that occurred from February 2001 to May 2003.

### Patients and Methods

#### Patients

Of 19 patients, 17 were males and 2 were females; their ages ranged from 15 to 47 years (mean age  $\pm$

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SD,  $32.7 \pm 4.92$  years). All patients had no history of glaucoma or ocular hypertension before silicone oil tamponade. Ocular hypertension was defined as intraocular pressure (IOP) of  $\geq 21$  mmHg. Sixteen patients were aphakic, and three patients had complicated cataract. The predisposing diseases (reasons for silicone oil tamponade) were traumatic proliferative vitreoretinopathy in 17 cases and rhegmatogenous retinal detachment in 2 cases. Acri-Sil-ol 5000 (Acri-tec, Germany) with high viscosity was used for silicone oil tamponade.

#### General Conditions

Silicone oil removal was performed 2 months to 2.3 years (mean  $\pm$  SD,  $17.25 \pm 3.16$  months) after silicone oil tamponade. Indications for silicone oil removal were silicone oil emulsification (in the vitreous and anterior chamber) in 9 eyes, secondary glaucoma in 7 eyes (combined with silicone oil emulsification in 5 eyes [emulsification was detected before silicone oil removal in 3, but it was discovered during silicone oil removal in 2]), and band-shaped corneal degeneration in 4 eyes. In two cases, silicone oil removal was performed  $>1$  year after silicone oil tamponade as a result of the patients' wishes, although no symptoms were identified. In all cases, silicone oil removal was performed via a pars plana entry. First, an infusion cannula was inserted into the vitreous cavity from an incision at the inferotemporal quarter 4.0 mm away from the limbus. Then another pars plana incision of 1.5 mm in length was made at the superotemporal quarter 4.0 mm away from the limbus. Depressing the posterior margin of the incision facilitated the silicone oil outflow. Silicone oil removal and pars plana lensectomy were done simultaneously on one eye with severe complicated cataract and silicone oil in the anterior chamber. Meanwhile, in the eyes with aphakia and in the eye that underwent silicone oil removal and pars plana lensectomy, the contents of the anterior chamber were also replaced with balanced salt solution. In the other two cases, no additional efforts were made to replace the aqueous humor, because no ob-

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vious silicone oil was found in the anterior chamber before silicone oil removal. At the end of the procedure, the incisions were closed with 6-0 silk suture.

Follow-up ranged from 21 to 49 days (mean  $\pm$  SD,  $35 \pm 6.35$  days) after silicone oil removal. IOP increased on day 2 to day 16 (mean  $\pm$  SD,  $7.89 \pm 2.75$  days) after silicone oil removal. IOP ranged from 26 to 48 mmHg (mean  $\pm$  SD,  $37.23 \pm 6.47$  mmHg).

Medical therapy was the primary mode of management for all patients with glaucoma. IOP in eight eyes remained uncontrollable even with administration of a combination of topical and systemic antiglaucoma agents. IOP in six eyes was practically controlled by local and systemic treatments. In the other five eyes, topical drugs were effective in reducing IOP to a normal level. Gonioscopy of 11 eyes revealed open angles in all 11. Of these 11 eyes, 9 had a few droplets of silicone oil on the iris surface and/or in the anterior chamber angle that were found by gonioscopy and slit-lamp examination. Slit-lamp examination of the other two eyes did not show any positive findings, while only gonioscopy demonstrated silicone oil drops hiding in the chamber angle. Gonioscopy was not performed on the remaining eight eyes, but slit-lamp examination was done. In these eight eyes, many silicone oil drops were discovered in the anterior chamber.

#### *Treatment of Secondary Glaucoma Due to Silicone Oil Retention*

Medical therapy was the primary management for all patients with glaucoma. Levobunolol, brimonidine, dorzolamide, and Xalatan (Parma, Belgium) were chosen and combined with acetazolamide or hyperosmolar agents, such as mannitol and glycerin, for effective control of IOP. IOP in 5 eyes was practically controlled to  $<25$  mmHg by topical medication. Of these five eyes, two had IOP in the normal range after discontinuation of all antiglaucoma agents, and three had IOP under control by medications; however, these three eyes were ultimately lost to follow-up after 1.5 months. The remaining 14 eyes with IOP ranging from 32 to 48 mmHg (mean  $\pm$  SD,  $38.35 \pm 2.93$  mmHg) underwent surgical intervention for control of IOP. Indications for surgical intervention were IOP of  $\geq 30$  mmHg for a 2- to 3-week observation period after discontinuation of systemic antiglaucoma medications and/or IOP of  $\geq 40$  mmHg after silicone oil removal that could not be controlled by topical medication in 1 to 2 weeks. Fourteen eyes underwent anterior chamber irrigation. A 2-mm penetrating incision at the 12-o'clock position of the superior limbus was made, followed by insertion of an irrigation-

aspiration cannula into the anterior chamber. At first, a "push-pull" technique was used to aspirate the large proportion of silicone oil droplets. To clear the silicone oil completely, a 7/16-inch needle was subsequently placed horizontally just over the surface of the iris, avoiding pointing directly toward the corneal endothelium, to wash out the silicone oil droplets. Finally, the needle was extended to the anterior chamber angle to clear the drops hidden in the angle.

#### **Results**

The mean IOP  $\pm$  SD was  $18 \pm 4.11$  mmHg without additional medical therapy after anterior chamber irrigation. The reductions in IOP were statistically significant ( $P < 0.05$ , paired *t*-test). Of 14 eyes, 9 had ideal IOP control (range, 12–20 mmHg). IOP ranged from 20 to 24 mmHg in 2 eyes after anterior chamber irrigation. IOP in the other 3 eyes was  $>25$  mmHg after anterior chamber irrigation. In two of these three eyes, silicone oil emulsification with severe ocular hypertension was present before anterior chamber irrigation. Finally, filtering surgeries were required in these two eyes, followed by IOP control in one eye and retinal detachment in one eye. The third eye with uncontrolled IOP after anterior chamber irrigation was found by gonioscopy to have quite a few silicone oil droplets in the anterior chamber angle postoperatively, which were removed after repeated anterior chamber irrigation and the ideal IOP was controlled.

Eleven eyes with resolved IOP after anterior chamber irrigation underwent gonioscopy 3 weeks after surgery. Except for negative findings for two eyes, a few silicone oil droplets remained in the anterior chamber angle in nine eyes. Of these nine eyes, six had silicone oil emulsification detected before anterior chamber irrigation.

#### **Discussion**

Doctors usually pay more attention to patients with increased IOP before silicone oil removal than to those with normal IOP preoperatively. As a result, the symptoms of secondary glaucoma may be regarded as postoperative inflammation, ultimately leading to damage of visual function. In our case series, 12 of 19 eyes had normal IOP before silicone oil removal. In the study by Wei et al,<sup>1</sup> IOP was elevated postoperatively in 11 of 64 cases of silicone oil removal, which indicates that secondary glaucoma is not a rare postoperative complication of silicone oil removal.

There are several major factors underlying this complication. First, there edema in the trabecular meshwork as a result of postoperative inflammation. Second, the mechanical impacts of balanced salt so-

lution during silicone oil removal may split the silicone oil droplets into much smaller drops, which more likely obstruct the trabecular meshwork (outflow pathway). IOP elevation often occurs 1 week after silicone oil removal. Such a phenomenon can be rationalized by blockage of the trabecular meshwork by silicone oil drops. It has been confirmed by pathologic examination that emulsified silicone oil drops or macrophage endocytosis with silicone oil drops can block the trabecular meshwork.<sup>2,3</sup> In addition, emulsified silicone oil droplets may be toxic to the trabecular cells and result in cellular degeneration. The silicone oil droplets become much smaller due to the striking effect of the solution during operation. Consequently, the smaller the drop is, the more likely it will obstruct the trabecular meshwork. According to Honavar et al,<sup>4</sup> silicone oil in the anterior chamber and silicone oil emulsification account for nearly 50% of cases of secondary glaucoma after silicone oil tamponade. Thus, complete removal of the silicone oil is critical to avoid such a complication.

On the basis of the findings of our case series, anterior chamber irrigation is effective in the treatment of secondary glaucoma caused by silicone oil retention. A penetrating incision at the superior limbus is recommended. The needle should be placed horizontally just over the iris surface, avoiding pointing directly toward the corneal endothelium, to wash out the silicone oil droplets. Moreover, to remove the silicone oil thoroughly, it must be emphasized that the needle should be placed deeper at the anterior chamber angle to clear away the drops hidden in the angle.

Control of IOP should be achieved in most cases after anterior chamber irrigation. Even if a few silicone oil droplets remain postoperatively, they might not definitely cause glaucoma. Patients with an elevated IOP should be followed up closely with proper medication therapy for 2 to 3 weeks. If IOP remains out of control, repeated anterior chamber irrigation is indicated. In our case series, there were nine cases of silicone oil retention after the first anterior chamber irrigation. Of these nine patients, six had silicone oil emulsification preoperatively, which implies that silicone oil removal should be performed before emulsification occurs. In addition, use of silicone oil with high purity and high viscosity is imperative to avoid silicone oil emulsification and the subsequent complications such as secondary glaucoma.

**Key words:** glaucoma treatment, silicone oil adverse effects, silicone oil postoperative complications.

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### UNUSUAL CLINICAL MANIFESTATION OF SCLEROCOROIDAL CALCIFICATIONS

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Scleral choroidal calcification is a well-known entity that has a spectrum of clinical manifestations and imaging abnormalities.<sup>1</sup> Although it may be seen in association with congenital or acquired disorders of calcium metabolism, hyperparathyroidism, renal failure, or Bartter–Gittelman syndrome, it most commonly presents as an idiopathic deposition of calcium in scleral and uveal tissue; typically, these calcifications are in the midperipheral retina in patients without underlying associated systemic disease.<sup>2</sup> The clinical manifestations vary, but they are usually nodular, yellowish-white thickenings or incomplete to complete rings of calcification in the vicinity of muscle insertions but also beyond both posteriorly and anteriorly.<sup>3</sup> We report a case in which there were essentially no clinical findings and uveal scleral calcification was incidentally detected by computed tomographic imaging of the orbits.

### Case Report

A 66-year-old woman was referred to our office because of an accidental finding of bilateral sclerocoroidal calcifications on an orbital computed tomographic scan obtained for chronic sinusitis

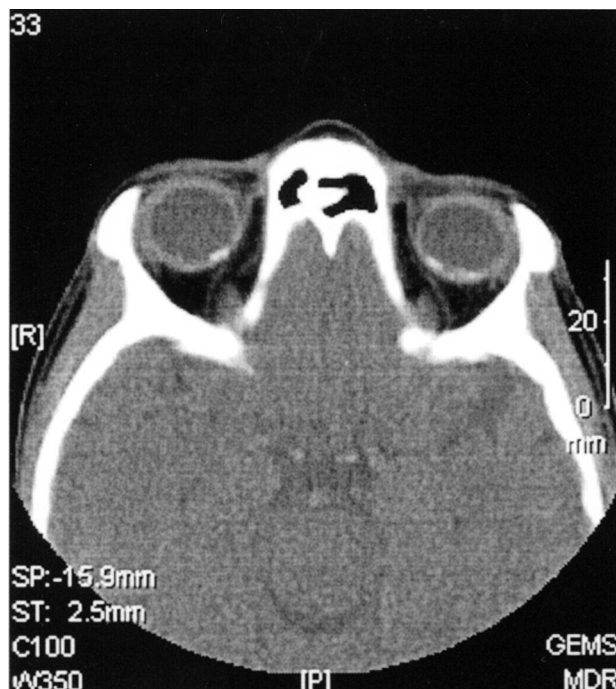
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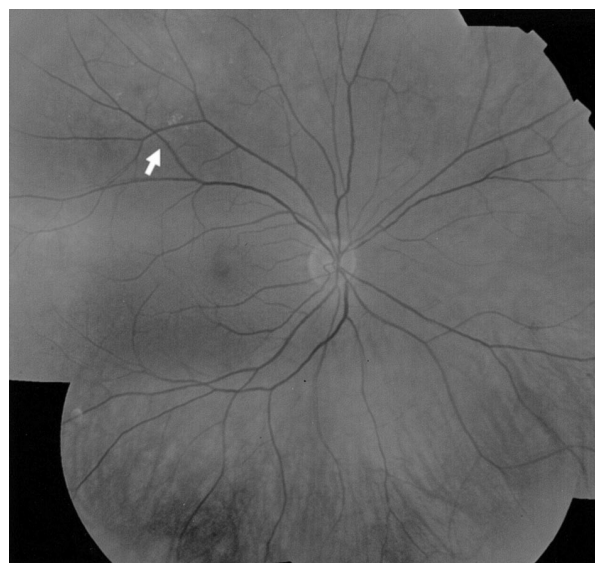
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**Fig. 1.** Computed tomographic scan of the orbits reveals several areas of sclerochoroidal calcification in both eyes.

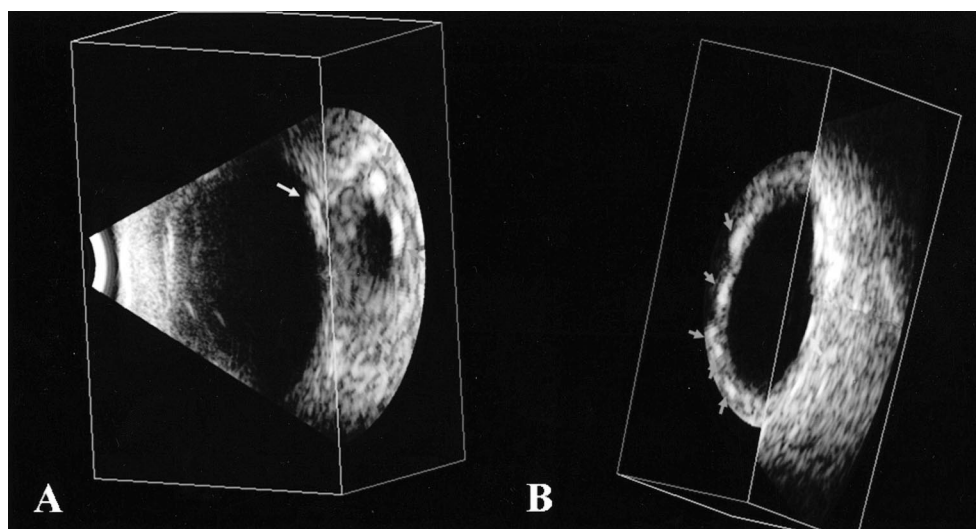
(Fig. 1). Her medical history was unremarkable. Visual acuity was 20/30 in the right eye and 20/25 in the left eye, and no typical manifestations of sclerochoroidal calcification were observed in the fundus; however, very subtle areas of atrophy were noticed in the superotemporal midperiphery of both eyes in the vicinity of a cluster of small drusen (Fig. 2). The presence of small sclerochoroidal calcifications was confirmed with ultrasound examination in the suspicious areas as well as in other locations (Fig. 3). The referring physician had already performed a complete systemic workup, and no conditions predisposing to sclerochoroidal calcification were found. The diagnosis of idiopathic sclerochoroidal calcification was made.



**Fig. 2.** A composite of color photographs of the right eye shows no typical signs of sclerochoroidal calcifications. In the superotemporal midperiphery, there are some areas of atrophy in the vicinity of a cluster of small drusen (arrow).

### Discussion

Uveal scleral calcification has been reported to occur rarely bilaterally in patients, although clinical manifestations were evident only unilaterally.<sup>4</sup> To our knowledge, this is the first case report of a patient in whom there were no clear clinically associated changes to indicate the presence of calcification in the eyes. Only because of imaging for sinusitis was calcification noted and also confirmed by B-scan ultrasonography. The findings in this case are consistent with the clinical impression shared by some posterior segment specialists that calcification in the choroid/sclera area is probably more com-



**Fig. 3.** Three-dimensional ultrasound images of the right (A) and left (B) eyes reveal multiple sclerochoroidal calcifications in both sagittal (yellow arrows) and coronal (green arrows) sections.

mon than originally considered, perhaps similar to a well-known aging change, the so-called “Cogan senile plaque” (which is seen more anteriorly in the sclera).<sup>5</sup> Again, the presence of calcifications in this patient appeared to have no association with ocular and systemic manifestations or ocular complications.

**Key words:** sclerochoroidal calcifications, ultrasound.

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### ACQUIRED UNILATERAL NIGHT BLINDNESS WITH NEGATIVE ERG: NINE-YEAR FOLLOW-UP

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At least 12 cases of a retinal disease called acquired unilateral night blindness have been reported.<sup>1–5</sup> These patients complain of a relatively acute onset night blindness only in one eye, and the dark-adapted electroretinograms (ERGs) in the affected eye often show a negative waveform. Fundus examinations and fluorescein angiograms are normal. The exact pathogenesis of this rare retinal disorder is unknown.

These patients often show spontaneous recovery of both the night blindness and abnormal ERGs after

several months.<sup>1,2,4</sup> We report a 30-year-old woman who presented with typical features of acquired unilateral night blindness. Her symptoms and abnormal ERG waveforms recovered very slowly, and returned to normal only after a prolonged period. Our immunologic results suggest that an autoantibody to a retinal protein may be involved in the etiology of this disorder.

### Case Report

A 30-year-old Japanese woman was referred to our hospital for unilateral night blindness of unknown cause. She noticed a sudden visual disturbance in night vision exclusively in the right eye. She had no systemic or ocular diseases including cancer and malignant melanoma, and family history revealed no other members to have any ocular diseases. At the initial examination, her corrected visual acuity was 20/10 in the right eye and 20/13 in the left. The fundus examination and fluorescein angiograms were normal (Figure 1). Visual fields were also normal by Goldmann perimetry in both eyes. Dark adaptation was tested by a Goldmann-Weekers adaptometer using an achromatic test target of 11 degrees, which was positioned at 15 degrees inferior of the visual field. The course of dark adaptation was normal in the left eye, but the final threshold was elevated by approximately 1.8 log units in the right eye. Subjective sensitivity profiles of the rod and cone visual systems were also tested by light-adapted and dark-adapted perimetry using a modified Humphrey Field Analyzer.<sup>6</sup> Rod and cone sensitivities were within normal range at all locations in the left eye, but rod sensitivities were severely reduced at all loci in the right eye. The dark/light ratios and base values of the electro-oculogram (EOG) were normal in both eyes without any significant difference between the right and left eye.

The full-field ERG was normal in the left eye, but the amplitude of the b-wave was reduced for both the rod and cone components in the right eye. The dark-adapted ERG elicited by a bright-flash stimulus showed a “negative” waveform (Figure 2A, upper trace).

To study the function of the cone ON- and OFF-pathways, photopic ERGs were recorded with a long-duration stimulus. The right eye showed a severely reduced ON-response b-wave with normal OFF-response d-wave (Figure 2B). These ERG findings suggested that the postphotoreceptor ON-pathways were predominantly affected for both the rod- and cone-pathways only in the right eye.<sup>3,4,7</sup> Based on these results, we diagnosed her with acquired unilateral night blindness.

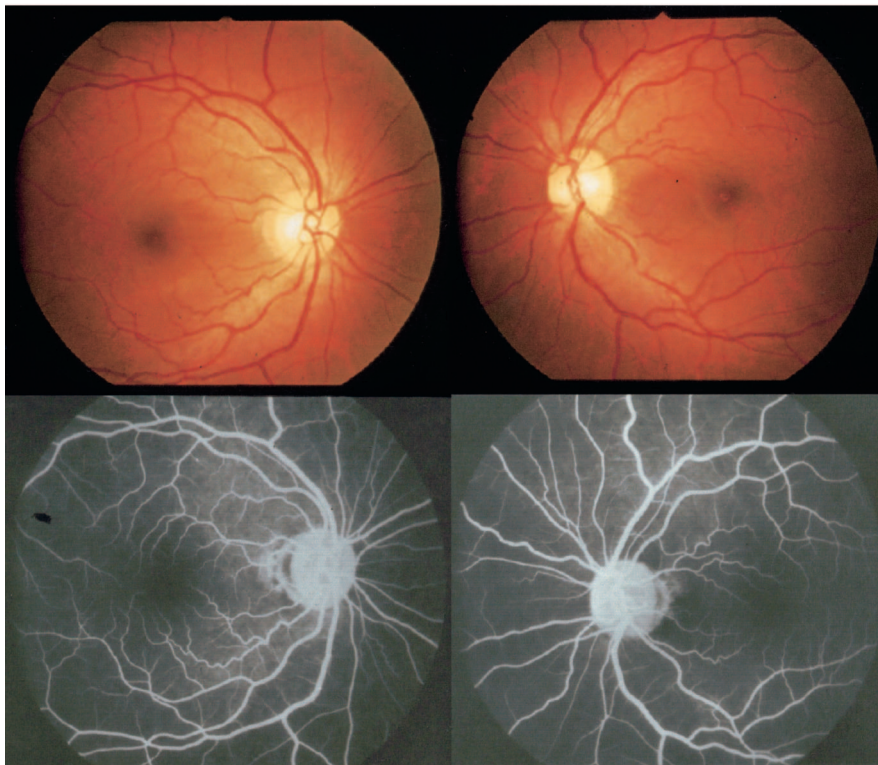
She was followed without any specific treatment. Her night blindness and abnormal ERG findings recovered very slowly. Four years after the onset, she still reported a difference in the vision in her two eyes, but her symptoms were improved. The amplitude of the ERG b-wave also recovered to 70% of the normal left eye, but it was still smaller than that of the a-wave (Figure 2A, middle trace). When next examined 9 years from the onset, her symptoms were essentially gone. The b-wave amplitude of the right eye was then equal to that of the left eye (Figure 2A, lower trace). These results indicated that a period between 5 to 9 years was required for this patient to recover to normal.

Western blot analysis was performed using bovine retinal proteins to determine whether there were any antiretinal antibodies in the sera of our patient. Two retinal proteins of approximately 105 kD (arrowhead 1) and more than 120 kD (arrowhead 2) were detected in the sera of this patient (Figure 3). We also examined sera from 10 normal individuals with same ethnic background as our patient, but these bands were not detected in any of them. We

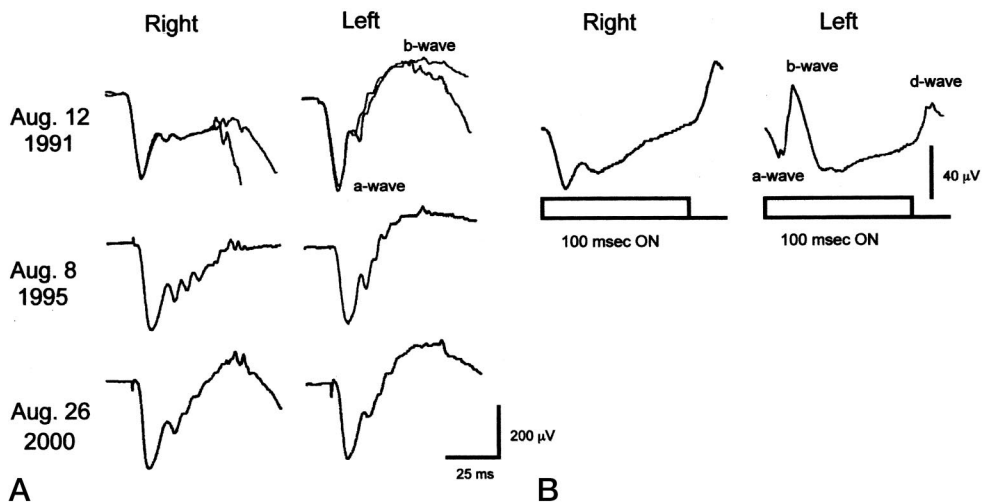
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Right Left

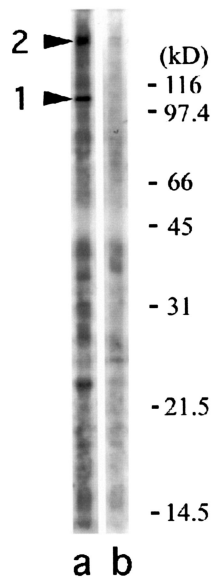


**Fig. 1.** Fundus photographs (upper) and fluorescein angiograms (lower) of 30-year-old woman with acquired unilateral night blindness. No abnormalities can be seen.



**Fig. 2.** Results of the full-field electroretinograms (ERGs). (A) Dark adapted ERGs with bright-flash stimulus recorded at initial examination, at 4 years after onset, and at 9 years after onset. Intensity of flash stimulus was 44.0 cd-s/m<sup>2</sup>. (B) Photopic ERGs with long duration (100 msec) stimulus at initial examination. Stimulus and background intensity were 200 cd/m<sup>2</sup> and 40 cd/m<sup>2</sup>, respectively.





**Fig. 3.** Results of Western blot analysis using bovine retinal protein. Bovine retinal proteins were resolved by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, blotted, and probed with patient's sera (lane a) and normal control serum (lane b). Two clear bands were detected in the patient's sera (arrowheads 1 and 2).

could not test other family members of this patient who were asymptomatic.

### Discussion

There are three prior reports on spontaneous recovery in patients with acquired unilateral night blindness.<sup>1,2,4</sup> Kelsey and Arden presented two patients with acquired unilateral night blindness with a negative ERG.<sup>1</sup> One of their patients, a 50-year-old woman, showed a sudden, spontaneous recovery of both symptoms and ERGs after 4 months. Ayaki et al presented a 23-year-old woman with acquired unilateral night blindness associated with negative ERG finding.<sup>2</sup> Her night blindness and abnormal ERG recovered to normal after 9 months. Murayama et al described a 46-year-old woman who also had acquired unilateral night blindness.<sup>4</sup> Her visual field defect and abnormal visual evoked potentials recovered to normal, but her ERG still showed negative waveform even 3 years after onset. To our knowledge, our patient had the longest recovery time, between 5 and 9 years. The reason why our patient required such a long period to recover is unknown, but it may be due to severity of her disease.

The exact etiology of this form of acquired night blindness is obscure. Fishman et al performed an immunologic examination in their patient with acquired unilateral night blindness, but no autoantibodies were found in the serum.<sup>3</sup> In our patient, Western

blot analysis demonstrated two clear bands as potential autoantigens in the sera. To our knowledge, this is the first case with acquired unilateral night blindness in whom autoantibodies were detected in the serum. This result suggested that autoantibodies to retinal protein may be involved in the etiology of this acquired disorder.

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### MACULAR HOLE FORMATION IN POSTVITRECTOMIZED EYES

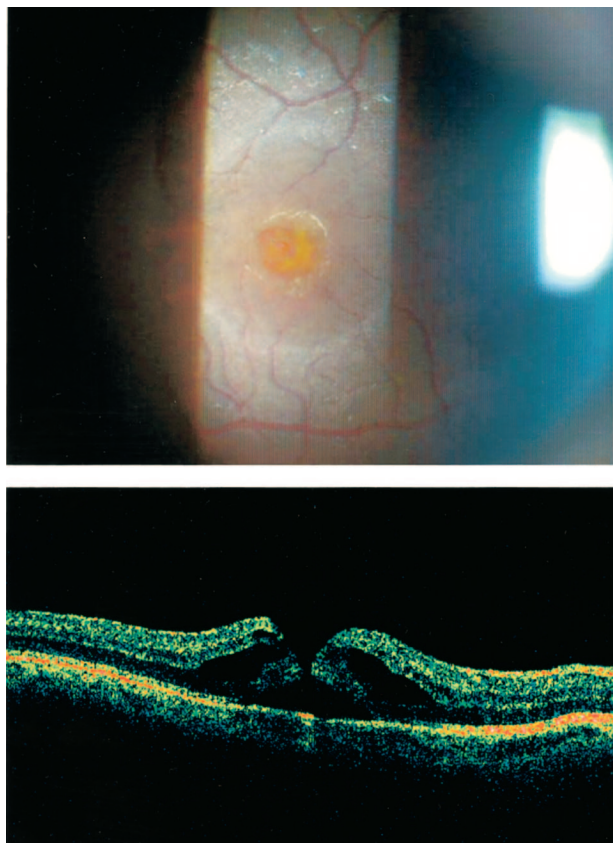
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The theory of tangential vitreous traction on the macula proposed by Gass<sup>1</sup> has been generally recognized as the pathogenesis of macular holes. Recently, optical coherent tomography (OCT) has demonstrated that anteroposterior traction exerted by vitreous fibers on the foveolar center plays an important role in the formation of a macular hole. Vitreomacular traction is considered an essential factor in the development of a full-thickness macular hole. We report on atypical cases of full-thickness macular holes that developed without apparent vitreomacular traction following vitreous surgery.

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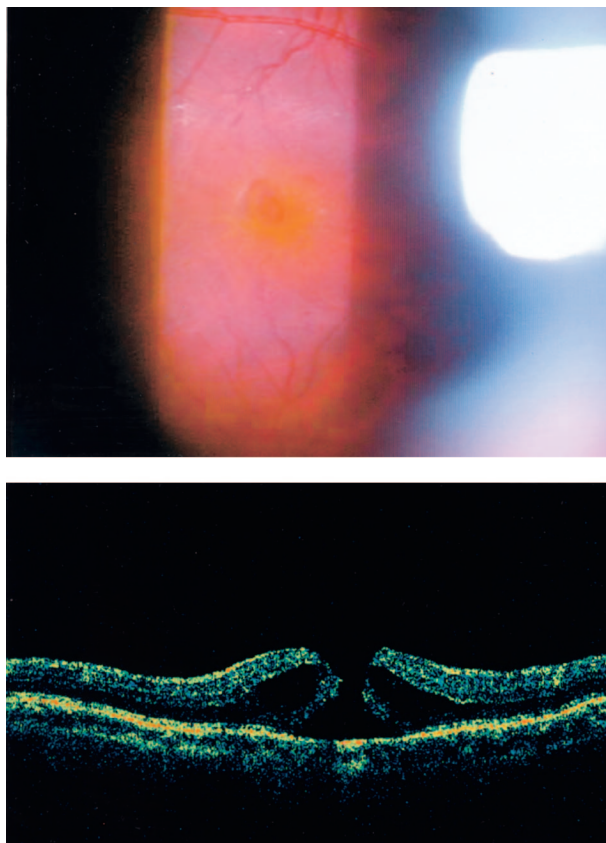
**Fig. 1.** Fundus photograph and optical coherence tomography of Case 1 at 36 months after the initial surgery. (Top) Fundus photograph reveals a small full-thickness macular hole with a fluid cuff. (Bottom) Optical coherence tomography shows a full-thickness hole without apparent vitreous cortex or epiretinal membrane.

### Case 1

A 75-year-old man presented at our clinic with floaters in his right eye on October 4, 2000. Mild cataract and posterior vitreous detachment were observed. His visual acuity was 20/25. The next day, he developed sudden visual loss in his right eye. Massive vitreous hemorrhage was observed, and the visual acuity had dropped to hand motion. Pars plana vitrectomy combined with cataract surgery was performed on November 1, 2000. Two retinal breaks were observed at the peripheral retina during surgery. Two weeks postoperatively, his visual acuity had improved to 20/20. Thirty-six months later, the patient had central scotoma and metamorphopsia in the right eye. Fundus examination and OCT showed a small full-thickness macular hole with a fluid cuff (Figure 1). The visual acuity was 20/40. Peeling of the internal limiting membrane (ILM) with use of triamcinolone acetonide (TA) and fluid-gas exchange were performed on December 2, 2003. During surgery, no apparent epiretinal membrane or residual vitreous cortex was observed around the macular hole. Two weeks after surgery, the macular hole was closed and the visual acuity was improved to 20/20.

### Case 2

A 60-year-old man was referred to our clinic for management of rhegmatogenous retinal detachment in his right eye. He had un-



**Fig. 2.** Fundus photograph and optical coherence tomography of Case 2 at 9 months after the initial surgery. (Top) Fundus photograph reveals a small full-thickness macular hole with a fluid cuff. (Bottom) Optical coherence tomography demonstrates a full-thickness hole with neither vitreous cortex nor epiretinal membrane.

dergone laser photocoagulation for a retinal tear in that eye 2 months before. A slit-lamp and ophthalmoscopic examination revealed a mild cataract and a bullous retinal detachment in his right eye. A retinal break was observed at 12 o'clock. The macula was not detached. His visual acuity was 20/20. Pars plana vitrectomy combined with cataract surgery was performed on March 24, 2003. During surgery, TA suspension was injected to observe a remnant of the vitreous cortex at the macula. A remnant of the vitreous cortex was noted at the macula as a white dot-like island and was removed with a retinal brush. Two weeks after surgery, the retina was reattached and the visual acuity was 20/16. Nine months after surgery, the patient had metamorphopsia in his right eye. Fundus examination and OCT revealed a small full-thickness macular hole in his right eye (Figure 2). The visual acuity had dropped to 20/60. He underwent pars plana vitrectomy with TA-assisted ILM peeling and fluid-gas exchange on January 19, 2004. No epiretinal membrane was observed around the macular hole during surgery. One month after surgery, the macular hole was sealed and the visual acuity was 20/20.

### Discussion

Our patients developed a full-thickness macular hole after vitreous surgery. During initial surgeries,

both eyes had shown a posterior vitreous detachment and no apparent vitreous traction on the macula. Recently, we have reported that vitreous cortex remnants at the macula were observed by using TA during surgery in patients with a rhegmatogenous retinal detachment.<sup>2</sup> In Patient 2, we observed residual vitreous cortex on the macula during surgery and removed it with a retinal brush because the vitreous cortex remnants may provide a scaffold for cellular proliferation, resulting in formation of epiretinal membrane. After vitreous surgery, both eyes developed a small full-thickness hole without apparent epiretinal membrane. The macular holes were closed successfully following ILM peeling and gas tamponade.

Smiddy reported nine cases of macular holes with atypical presentations.<sup>3</sup> Two of them developed a full-thickness macular hole after vitrectomy for epiretinal membrane removal. Lipham and Smiddy reported three other cases who presented full-thickness macular holes that developed 10 months to 5.5 years after previous vitrectomy.<sup>4</sup> The three cases occurred long after vitreous removal, and had no evidence of any residual cortical vitreous. In our patients, the macula was basically intact at the initial surgery. No residual vitreous cortex or epiretinal membranes on the macula were observed during the second surgery. In this subset of patients, vitreofoveal traction does not seem to have played a role in macular hole formation. Smiddy and others proposed that a degenerative process in inner retinal surface initiated the spontaneous umbo dehiscence.<sup>4,5</sup> Glial migration may proceed along the retinal surface through the umbo dehiscence. The umbo dehiscence may not be closed and glial contraction may result in enlargement of the macular hole. Presumably, the same pathogenetic process could occur in our patients. The macular holes were successfully closed since the glial proliferation around the hole may have been removed by the peeling of the ILM.

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### IS TAMOXIFEN A RISK FACTOR FOR RETINAL VASO-OCCLUSIVE DISEASE?

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Tamoxifen is an estrogen receptor modulator used in the treatment of breast cancer, both as a valuable adjuvant and as a chemoprevention agent. Concerns have been raised about the potential complications of this medication, including increased risk of endometrial carcinoma and thromboembolic disease.<sup>1</sup> We previously evaluated the potential ocular toxicity of tamoxifen in a study sponsored by the National Cancer Institute through the National Surgical Adjuvant Breast and Bowel Project (NSABP) by using single-masked, treatment and placebo cohorts. We documented a low risk of retinal toxicity and an unexpected increased prevalence of posterior subcapsular cataracts.<sup>2</sup> After our initial report, verification of the increased incidence of cataracts was obtained from the reports of ocular adverse effects from the NSABP-sponsored Breast Cancer Prevention Trial (BCPT; P-1).<sup>3</sup>

A number of questions remain regarding the potential risks of tamoxifen to the eye.<sup>4</sup> A major question is whether the previously demonstrated increased risk for systemic large vessel thromboembolic disease would be similarly observed for retinal small vessel occlusive disease (RVOD). RVOD is defined as a partial or total occlusion of one or more arterioles or

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Table 1. BCPT Participants Experiencing Retinal Vaso-occlusive Disease (RVOD)

Characteristics	Placebo	Tamoxifen	Total
Total number of individuals with RVOD	8	11	19
Age at diagnosis, yr			
Mean	60.6	59.9	60.2
SE mean	2.8	2.5	1.8
Range	48 to 71	45 to 70	45 to 71
Time on study at diagnosis of RVOD, yr			
Mean	1.8	3.7	2.9
SE mean	0.6	0.5	0.4
Range	0.2 to 4.6	0.3 to 5.4	0.2 to 5.4
Type of RVOD (ICD-9 code)			
Retinal vascular, unspecified (362.30)	1	4	5
Central retinal artery (362.31)	0	1	1
Arterial branch (362.32)	2	0	2
Partial arterial (362.33)	0	1	1
Transient arterial (362.34)	2	3	5
Central retinal vein (362.35)	0	0	0
Venous branch (362.36)	2	2	4
Venous engorgement (362.37)	1	0	1

BCPT = Breast Cancer Prevention Trial; ICD = International Classification of Diseases.

venules of the retina. Therefore, we have reviewed the adverse effects data from the BCPT; P-1 to evaluate and report the incidence of retinal vascular events in both the treatment and control groups.

### Subjects and Methods

A total of 13,204 subjects participated in the BCPT with a range of follow-up of 3 to 70 months (mean = 47.7 months). The composition of the study population has been described elsewhere.<sup>3</sup> The placebo and treatment groups were randomly assigned and included 6,608 and 6,596 participants, respectively. The eye examinations were not regularly scheduled and the reports were generated as a result of patient symptoms (adverse event reporting) and self-referral for evaluation. Although the women participating in the BCPT trial were strongly encouraged to have regular eye care during their participation, no formal ophthalmic evaluation was included as part of the study design. Each ocular event was reported to the BCPT Study Center and ophthalmic and/or optometric records were obtained in every instance and reviewed by M.B.G. If the diagnosis was ambiguous, then additional data were sought. None of the subjects was directly examined by the authors and no additional diagnostic testing or photography was requested to confirm the original assessment by the subject's eye care provider. The reports were further classified into specific etiologies of ocular events, of which only the retinal vaso-occlusive lesions are included in this report.

The number of women experiencing retinal vaso-

occlusive lesions was tabulated and the average annual incidence rates per 1,000 person-years were calculated by treatment group. The relative risk and 95% confidence intervals on the relative risk were determined. The relative risk was expressed as a ratio of the incidence rate in the tamoxifen group to the rate in the placebo group. To evaluate the statistical significance of the difference between the rates by treatment group, the *P* value was determined using the exact binomial test using the ratio of the observed person-years for each treatment group as the expected proportion.

### Results

During the course of participant follow-up, over 30,000 eye examinations were reported by a total of 10,758 participants. The types and distribution of cases of retinal vascular events are presented in Table 1. The different forms of RVOD were too infrequent for individual statistical analyses. When considered in aggregate, these lesions showed no statistical evidence ( $P = 0.32$ ) of an increased incidence in the tamoxifen-treated cohort (11 cases) as compared to the incidence in the control group (8 cases). The average annual rates per 1,000 of retinal vaso-occlusive lesion were 0.29 and 0.40, respectively. The relative risk of a vaso-occlusive event associated with tamoxifen was 1.37 with a 95% confidence interval of 0.50 to 3.93. As shown in Table 1, the mean time on study at diagnosis of RVOD was twice as long in the tamoxifen group as compared to the placebo group, provid-

Table 2. RVOD Incidence and Relative Risk Among BCPT Participants Based on Tamoxifen Exposure and Potential Risk Factors

Potential Risk Factor Present at Baseline	Number of Participants in Study Cohort		Number of Participants Diagnosed With RVOD		Annual Incidence Rate per 1000		Relative Risk (95% CI)
	Placebo	Tamoxifen	Placebo	Tamoxifen	Placebo	Tamoxifen	
Diabetes Hx							
No	6348	6319	7	10	0.27	0.38	1.43 (0.49, 4.44)
Yes	260	277	1	1	1.04	0.93	0.89 (0.11, 69.57)
Smoking Hx*							
None	3648	3573	3	8	0.20	0.53	2.69 (0.64, 15.79)
Current	817	834	0	0	0	0	—
Former	2129	2172	5	3	0.57	0.34	0.59 (0.09, 3.02)
Hypertension Hx							
No	5139	5132	4	7	0.19	0.33	1.76 (0.45, 8.22)
Yes	1469	1464	4	4	0.69	0.67	0.97 (0.18, 5.19)
Glaucoma Hx							
No	6480	6484	7	11	0.26	0.41	1.56 (0.55, 4.76)
Yes	128	112	1	0	1.92	0	—
Total	6608	6596	8	11	0.29	0.40	1.37 (0.50, 3.93)

\* Smoking status was unknown for 14 placebo and 17 tamoxifen participants.

BCPT = Breast Cancer Prevention Trial; RVOD = retinal vaso-occlusive disease; 95% CI = confidence interval; Hx = history.

ing further support to our observation of no increased risk for RVOD from tamoxifen use.

To assess the possibility that the risk of RVOD may be significantly elevated among a subset of tamoxifen participants who may have had some predisposing risk factors for RVOD, the data were evaluated by baseline status regarding history of smoking, diabetes, hypertension, and glaucoma (Table 2). The relative risks for all categories of these parameters were not statistically significant and all the corresponding 95% confidence intervals spanned a relatively broad range that included 1.00.

Overall, the placebo and tamoxifen-treatment study groups were very similar with respect to the frequency of potential systemic and ocular risk factors for thrombosis, such as diabetes, smoking, hypertension, and glaucoma (Table 2). Differences between the frequencies of these risk factors between the two groups of subjects who experienced RVOD were not significant given the few individuals. We combined the cases from the placebo and tamoxifen-treated cohorts to determine the relative risks of the reported factors for RVOD. As shown in Table 3, the relative risks of 3.02, 2.64, and 3.11 were observed in the presence of diabetes mellitus, hyperten-

Table 3. RVOD Incidence and Relative Risk Among BCPT Participants Relative to Potential Risk Factors, Irrespective of Tamoxifen Exposure

Potential Risk Factor Present at Baseline	Number of Participants in Study Cohort	Number of Participants Diagnosed With RVOD	Annual Incidence Rate per 1000	Relative Risk (95% CI)
Diabetes Hx				
No	12,667	17	0.33	1.00
Yes	537	2	0.98	3.02 (0.34, 12.70)
Smoking Hx*				
None	7221	11	0.37	1.00
Current/former	5852	8	0.33	0.91 (0.32, 2.47)
Hypertension Hx				
No	10,271	11	0.26	1.00
Yes	2933	8	0.68	2.64 (0.92, 7.20)
Glaucoma Hx				
No	12,964	18	0.34	1.00
Yes	240	1	1.05	3.11 (0.07, 19.70)

\* Smoking status was unknown for 31 participants.

BCPT = Breast Cancer Prevention Trial; RVOD = retinal vaso-occlusive disease; 95% CI = confidence interval; Hx = history.



sion, and glaucoma, respectively. These values are consistent with the previous reports, although none of them is statistically significant given the few participants with RVOD.<sup>5,6</sup>

### Discussion

The association of tamoxifen with large vessel thromboembolic events (especially venous thrombosis) has been established by multiple studies.<sup>1</sup> A similar association observed with estrogen therapy (oral contraceptives and postmenopausal hormone replacement therapy) has led some to consider that these medications may also pose an increased risk for retinal vascular occlusions.<sup>7</sup> However, some studies suggested that tamoxifen may actually lower the risk of myocardial infarction and arterial thrombosis due to its beneficial effects on cardiovascular status resulting from its mild estrogen-like activity.<sup>3,8</sup> One study implicated adjuvant tamoxifen therapy as the cause of thrombotic angiopathy of the retina in one case, although this could only be a coincidental occurrence.<sup>9</sup>

The reporting of ocular events in the BCPT trial may represent an underestimate of incidence, because these reports were generated as a result of patient symptoms and self-referral for evaluation. However, the women in the BCPT trial were strongly encouraged to have regular eye care during their participation and it is reasonable to expect that this highly motivated research cohort were probably more attentive to their health and more likely to seek medical attention than the regular population. The BCPT; P-1 data reflect the known increased risk of large vessel thromboembolic disease associated with tamoxifen therapy with an average annual incidence rate per 1,000 of 0.84 in the placebo population and a relative risk ratio of 1.60 comparing the rate in the tamoxifen population to that in the placebo population. The differences between the placebo and treated groups exhibited borderline statistical significance at a *P* value of 0.057.<sup>3</sup> We estimate that the BCPT data can provide a statistical power of only 0.27 to detect a statistically significant relative risk of RVOD comparable to that seen for large vessel thromboembolic disease (1.60). With the rate of retinal occlusive disease observed in the placebo group (0.3 per 1,000), the relative risk that would be detectable as statistically significant with 0.80 statistical power would have to be 2.6 or greater. The much smaller relative risk noted in this trial is consistent with that due to chance. Furthermore, the low rate of RVOD among those in the tamoxifen group should provide some reassurance to those taking this therapy, since it appears to be lower than that associated with other known risk factors such as hypertension and glaucoma.

The predominate information in the literature regarding possible ocular effects of tamoxifen comes from case reports. One must view any efforts to establish a causal relationship of tamoxifen with retinal vaso-occlusive disease from such information with a great deal of caution. Given the widespread use of the medication, speculations of associations based on isolated case reports (even with a sound biologic hypothesis) are unwarranted. The evaluation of the effects of any drug requires a sufficient sample size and a masked controlled study to unambiguously establish its safety and complication profile.

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### INTRAOPERATIVE RADIOGRAPHIC DETECTION OF A “LOST” SCLERAL PLUG

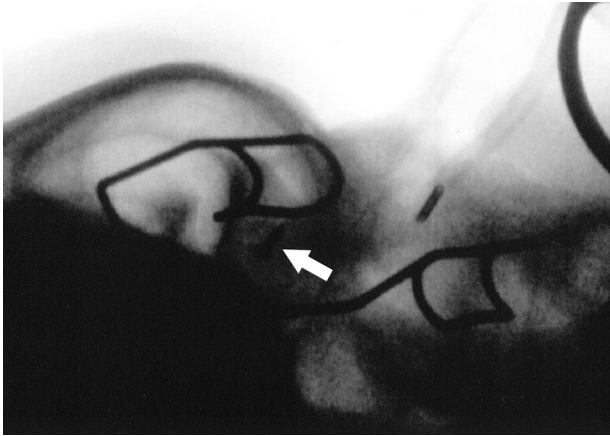
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Modern pars plana vitrectomy surgery involves frequent instrument passes through 20-gauge sclerotomies. Maintaining constant intraocular volume and pressure, while

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**Fig. 1.** The white arrow on this intraoperative x-ray points to the retained scleral plug in a superior quadrant.

performing indirect ophthalmoscopy or securing a scleral buckle, requires temporary closure of the sclerotomies with stainless steel plugs.<sup>1</sup> Traumatically enlarged sclerotomies decrease scleral friction, facilitating unplanned expulsion of the plugs.<sup>2</sup> Deformation of the globe and traction suture movement may inadvertently dislodge a plug, sometimes without the surgeon's knowledge. In an eye with extensive conjunctival dissection, the plug may fall into the posterior sub-Tenon's space. Often the surgeon is confronted with the question of whether the plug has flown off the surgical field or fallen into the orbit.

The following case describes a "lost" plug that escaped initial detection, but was easily recovered from the orbit after its discovery with an intraoperative x-ray.

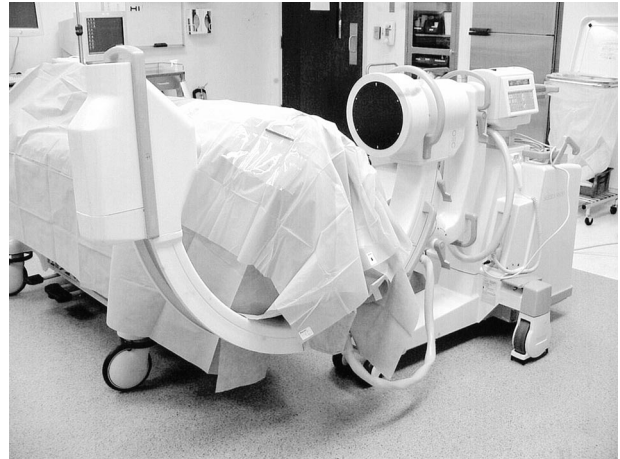
### Case Report

A 62-year-old man underwent vitrectomy, air-fluid exchange, and scleral buckle surgery for a rhegmatogenous retinal detachment. During placement of a circumferential scleral buckle, the superior-nasal scleral plug dislodged. Initial attempts to locate it, both behind the eye and off the surgical field, were unsuccessful.

A sagittal orbital x-ray with a c-arm digital mobile imaging system (GE OEC Medical Systems, Series 9,800) showed a scleral plug 1" superior and posterior to the infusion cannula (Figure 1). Guided by the x-ray findings, a directed search easily recovered the plug posterior to the equator in the superior-nasal quadrant.

### Discussion

Introduced over 2 decades ago, scleral plugs are routinely used during complex vitreoretinal surgeries. Extruded plugs remaining on the surgical field will fall either inside or outside the conjunctiva/Tenon's tissue complex. Plugs outside this layer reside within recessed fornix and are easily discovered with peritomy closure at the conclusion of surgery. However, plugs inside this complex often migrate posterior to the globe and may be missed by the surgeon. To help



**Fig. 2.** A mock-up of the intraoperative technique shows the c-arm digital mobile imaging system performing a sagittal x-ray of the orbit.

locate dislodged plugs, attached suture modifications were developed.<sup>3</sup> Retained stainless steel plugs in the posterior sub-Tenon's space may be well tolerated, although the medical-legal implications of retained plugs are unknown.

Gibran and Kinsella suggested that since plugs are both radio-opaque and ferromagnetic, magnetic resonance imaging evaluation of a patient with a retained plug is contraindicated because of the risk of its movement through the orbit. They recommended postoperative x-rays of patients who experienced lost plugs during surgery.<sup>4</sup> With the growing importance of magnetic resonance imaging in modern medicine, vitreoretinal surgeons should strive to prevent inadvertent plug retention.

The c-arm radiographic technique enables the intraoperative detection of a retained plug without compromising the sterile surgical field (Figure 2). The sagittal projection minimizes bone shadow and maximizes the contrast between the plug and soft tissue.

Surgeons confronted with a missing plug may consider this intraoperative radiographic technique to avoid inadvertent retention.

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## INTRAVITREOUS TRIAMCINOLONE SIMULATING FROSTED RETINAL ANGIITIS

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Intravitreal triamcinolone acetonide (TA) is becoming a standard of medical care in the management of intraocular inflammatory, retinal vascular occlusive, and intraocular vasogenic diseases.<sup>1–3</sup> This emerging treatment modality has assumed a prominent role in the management of such diseases, in spite of the absence of clinical trials to support its efficacy and safety. In this brief report, we present two cases in which intravitreal TA simulated frosted retinal angiitis: one case in a patient

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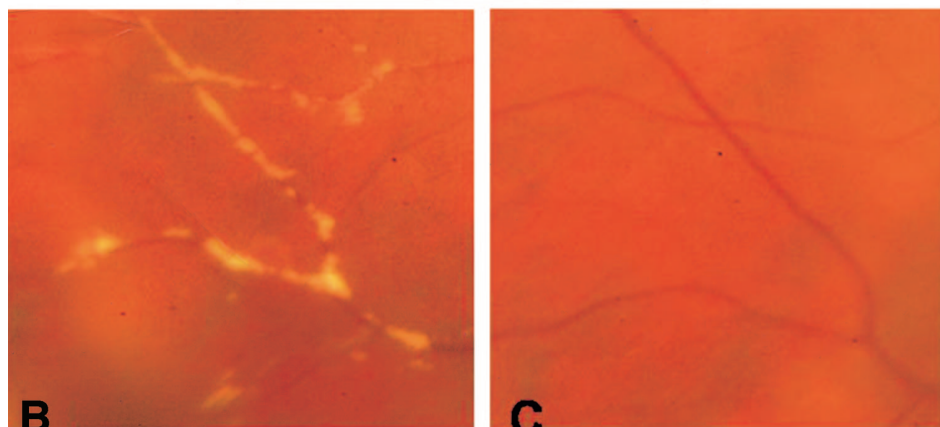
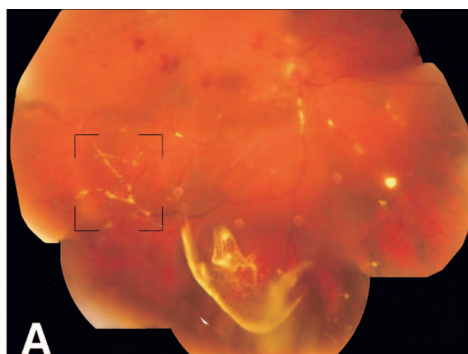
with macular edema secondary to a branch retinal vein occlusion and the other in a patient with neovascular age-related macular degeneration.<sup>2,4</sup>

### Case 1

A 71-year-old man presented with vision loss in the right eye secondary to supratemporal branch retinal vein occlusion. Best-corrected visual acuity was 20/40. Two weeks later, visual acuity decreased to 20/80. Slit-lamp biomicroscopy and optical coherence tomography revealed worsening of the macular edema. Contact B-scan ultrasonography demonstrated a complete posterior vitreous detachment. The patient was treated with an intravitreal injection of 4 mg of TA. One day later, he presented with TA deposition on both retinal arteries and veins in conjunction with TA suspension in the vitreous. Two weeks later, these depositions disappeared, and the best-corrected visual acuity was 20/60. (Fig 1)

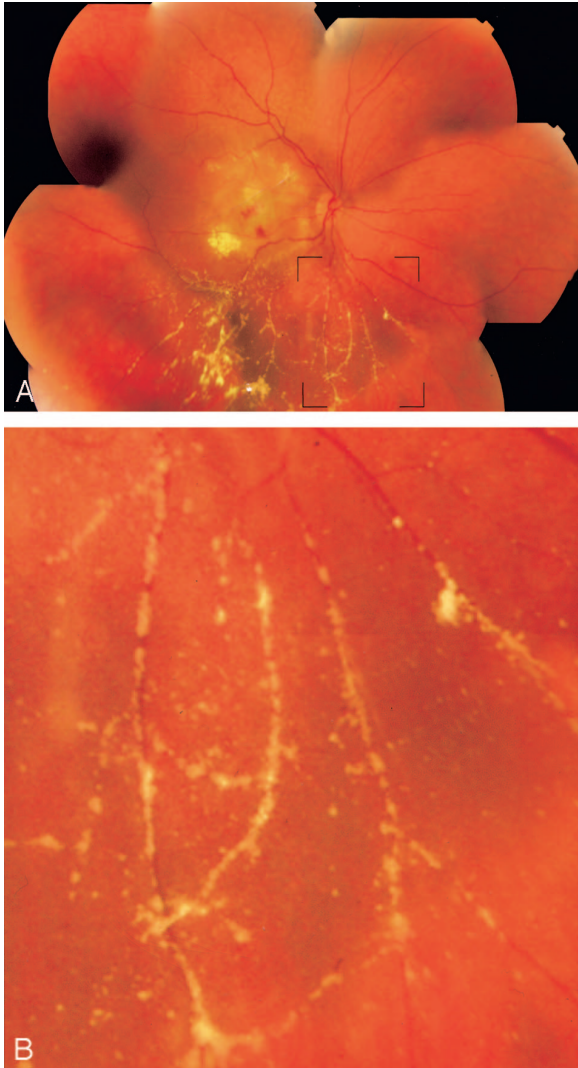
### Case 2

A 78-year-old woman had vision loss in the right eye. She was diagnosed with a retinal angiomatous proliferation lesion in that eye. Shortly thereafter, an occult neovascular membrane occurred in the left eye. Best-corrected visual acuity was 20/100 in the right eye and 20/50 in the left eye. The patient was treated with juxtасcleral anecortave acetate in the right eye as per an institutional review board–approved study protocol. Six months later, visual acuity declined to 20/320. Thus, the patient received an intravitreal injection of TA (4 mg). The next day, TA particle deposits along both retinal arteries and veins were evident. Two weeks later, the patient returned with stable vision, and the TA particles had disappeared. (Fig 2)



**Fig. 1.** Case 1. **A**, Composite color fundus photograph of a patient with branch retinal vein occlusion 1 day after intravitreal triamcinolone acetonide (TA) injection that shows TA deposition on both retinal arteries and veins in conjunction with TA suspension in the vitreous. **B**, Magnified view of the bordered area in **A** demonstrates TA deposition on both retinal arteries and veins. **C**, Color photograph of the same magnified area reveals the resolution of retinal vessel deposition 2 weeks after treatment.





**Fig. 2.** Case 2. **A**, Composite color fundus photograph of a patient with retinal angiomatous proliferation that shows triamcinolone acetonide (TA) deposition on both retinal arteries and veins 1 day after TA injection. **B**, Magnified view of the marked area in **A** demonstrates TA deposition on both retinal arteries and veins.

### Discussion

There have been several studies in the ophthalmic literature discussing the use of TA in the management of retinal edema, secondary to venous occlusive disease, for chronic uveitis, and for diabetic retinopathy.<sup>1–3</sup> The drug has also been used in the management of choroidal neovascularization, particularly in treating age-related macular degeneration.<sup>4</sup> Although the safety and efficacy of intravitreal TA have not yet been substantiated by large clinical trials, its use is widespread among retina specialists. Well-known complications include cataract formation, glaucoma, retinal detachment, and sterile as well as infectious

endophthalmitis. In the cases reported, we observed an affinity of the TA particles along the retinal vasculature (both venules and arterioles). This was not associated with any adverse effect. The precise mechanism for what is causing this deposition of crystals around the retinal vessels is not clearly understood. We can speculate about some possible explanations.

First, TA accumulates at the margins of posterior hyaloidal detachment, but this does not explain the drug adherence to the retinal blood vessels themselves, unless residual vitreous material is present on the vessels themselves causing adherence of the crystals.<sup>5</sup> Second, macrophages could engulf the crystals and migrate to the perivascular spaces. This happens in diseases like retinitis pigmentosa, where retinal pigment epithelium cells accumulate in a cuff around retinal vessels leading to bone spicule pigmentation.<sup>6</sup> Third, another possible explanation of the dispersion of TA molecules along the course of the larger retinal vessels may involve an affinity of the drug to common ubiquitous extracellular molecules like fibrin. This could be more evident in the space surrounding retinal blood vessels. Finally, another explanation may involve intraocular fluid dynamics: the drug may be in a physiologic state governed by vitreous–retinal–choroidal cellular transport mechanisms.

In any event, the deposition of TA along the blood vessel walls appears to have no deleterious effect on the eventual outcome. As our case reports demonstrate, some patients may present after intravitreal TA injection with a clinical appearance similar to that of frosted angiitis; these patients need only be managed conservatively with standard clinical surveillance, until the particles are reabsorbed.

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## SUBMACULAR PLACOID PIGMENT EPITHELIAL ALTERATION AFTER RESOLUTION OF MACULAR EDEMA IN CENTRAL RETINAL VEIN OCCLUSION

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Central retinal vein occlusion (CRVO) is a common retinal vascular disorder frequently associated with severe vision loss. Opremcak et al<sup>1</sup> reported that surgical decompression of CRVO via radial optic neurotomy (RON) was associated with improved appearance of the retina in all eyes and stabilization or improvement in visual acuity. Intravitreal injection of triamcinolone acetonide has been reported to cause a decrease in the amount of macular edema in CRVO.<sup>2</sup> We describe six patients with ischemic CRVO, of whom five underwent RON. Due to persistent macular edema in all cases, intravitreal triamcinolone was given at a later time. All patients had dramatic improvement in macular edema but had less than satisfactory improvement in visual acuity. Each patient developed a single discrete region of increased pigmentation in the central macula after rapid resolution of the edema and subretinal fluid.

### Patients and Methods

In this retrospective descriptive study, six patients with severe CRVO and markedly compromised visual acuity were included. In five cases, RON was per-

formed. Patients were evaluated with determination of best-corrected visual acuity, ophthalmoscopy, optical coherence tomography (OCT), and fluorescein angiography before surgery. No patient had any apparent collateral circulation at baseline. RON was performed by standard three-port vitrectomy using a specially designed knife (Spaide CRVO knife, Dutch Ophthalmics USA, Kingston, NH). There were no surgical complications. Patient 6 underwent panretinal laser photocoagulation. Due to persistent macular edema associated with poor visual acuity, 4 mg of triamcinolone acetonide (Kenalog, Bristol–Meyers–Squibb, Princeton, NJ) was injected intravitreally 2 months to 6 months after prior intervention.

### Results

There were three females and three males. The mean age  $\pm$  SD of the patients was  $67.5 \pm 14.5$  years (Table 1). The mean CRVO duration before treatment was  $2.4 \pm 1.0$  months. The preoperative visual acuity ranged between 5/400 and 20/400. In all eyes, macular edema and serous detachment of the neurosensory retina were documented preoperatively by OCT. Postoperatively, fundus examination and fluorescein angiography showed improved caliber of retinal vessels and resolution of intraretinal hemorrhages. OCT revealed persistent macular edema associated with serous detachment of the neurosensory retina in all eyes after RON or laser treatment (Table 2). In all RON cases, retinochoroidal collateral veins at the disk in the area of the neurotomy were identified by indocyanine green angiography. The time from RON or laser treatment to triamcinolone acetonide injection ranged from 2 months to 6 months (mean  $\pm$  SD,  $2.9 \pm 1.6$  months). After the initial triamcinolone injection, complete resolution of intraretinal fluid and neurosensory detachment was documented by OCT in three cases. In three eyes, the remaining macular edema was noted, which responded to repeated triamcinolone injection after 3, 5, and 6 months. After injection, the patients were observed initially at 2- to 3-week intervals. The mean follow-up after initial treatment  $\pm$  SD was

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Table 1. Patient Data

Patient	Age (y)	Sex	Eye	HTN	IHD	Diabetes Mellitus	Duration of CRVO (mo)
1	63	F	OD	+	–	–	3
2	42	M	OS	–	–	–	3
3	70	M	OS	–	+	–	1
4	80	M	OS	+	+	–	1.25
5	68	F	OD	+	+	–	3
6	82	F	OD	+	+	–	3

HTN, hypertension; IHD, ischemic heart disease; CRVO, central retinal vein occlusion; +, present; –, absent.

Table 2. Postoperative Results after RON or PRP and Intravitreal Triamcinolone Injection for Patients With Central Retinal Vein Occlusion

Patient	Initial VA	Initial Procedure	ME	ND	VA After RON or PRP	Interval From RON/PRP to TA (mo)	After TA			Second TA	After Second TA			Onset of Pigment After TA (wk)	Final VA	Final Visit		FU (mo)
							ME	ND	VA		ME	ND	VA			ME	ND	
1	5/400	RON	+	+	2/400	2.5	-	-	5/400	-				5	10/400	-	-	16
2	20/400	RON	+	+	5/400	2	-	-	20/400	-				6	20/400	-	-	15
3	20/400	RON	+	+	5/400	2	+	+	20/400	+	-	-	20/100	3	20/200	-	-	9
4	5/400	RON	+	+	6/400	2	+	+	8/400	+	-	-	20/320	3	20/320	-	-	8
5	20/400	RON	+	+	20/200	6	-	-	20/200	-				3	20/200	-	-	8
6	5/400	PRP	+	+	5/400	3	-	-	20/400	+	-	-	20/400	4	20/400	-	-	11

RON, radial optic neurotomy; PRP, panretinal photocoagulation; VA, visual acuity; ME, macular edema; ND, neurosensory detachment; TA, triamcinolone acetate; FU, follow-up; +, present; -, absent.

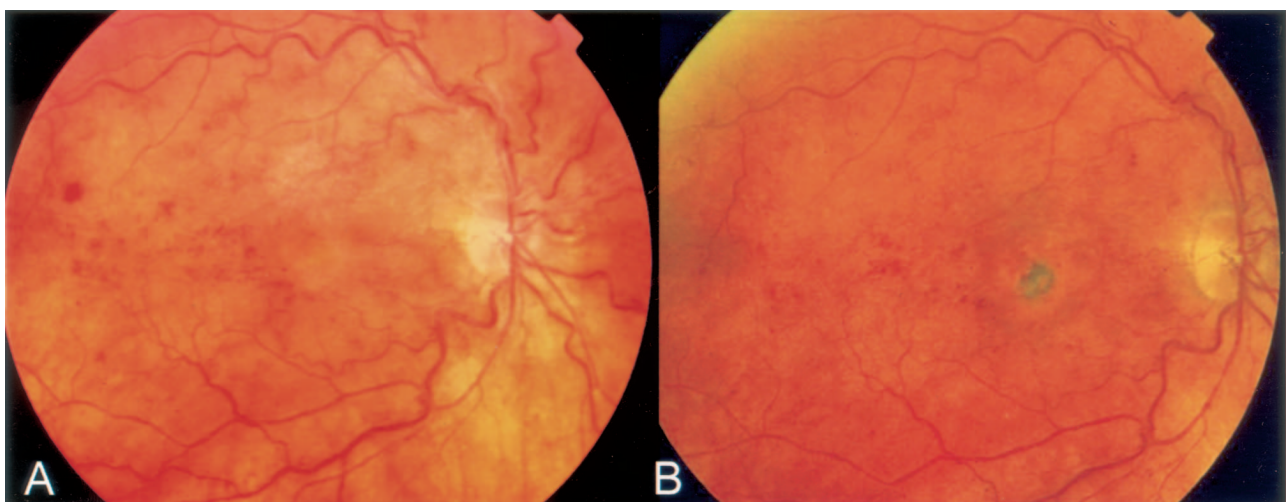
11.2 ± 3.5 months. At the final follow-up, visual acuity improved in 2 patients to 20/200 and was stable in 4 patients. In all cases, OCT did not detect any subretinal fluid or retinal edema at the final visit.

All patients had an area of increased pigmentation at the level of the retinal pigment epithelium (RPE) that was ≈0.5 disk diameter in size and located under the central macula, which was noticed between 3 weeks and 6 weeks after triamcinolone injection (mean ± SD, 4 ± 1.3 weeks) (Fig. 1). OCT of this area revealed an area of thickened RPE (Fig. 2). Fluorescein as well as indocyanine green angiography demonstrated the absence of choroidal neovascularization within the region of increased pigmentation. Autofluorescence photography showed that the area of hyperpigmentation was highly autofluorescent, suggesting the presence of lipofuscin. No neovascularization in the anterior or posterior segment developed

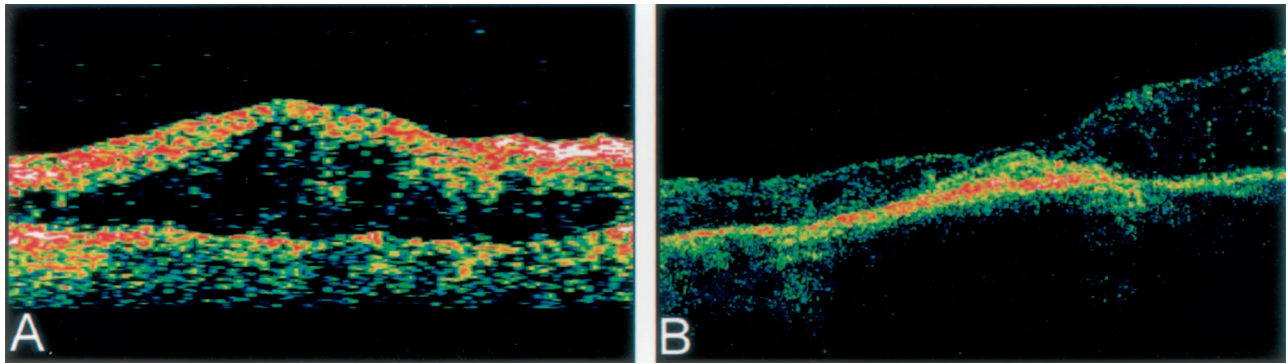
elsewhere during follow-up. One patient treated with RON and intravitreal triamcinolone injection had a history of an old untreated CRVO in her fellow eye that also demonstrated a central area of increased pigmentation (Fig. 3).

### Discussion

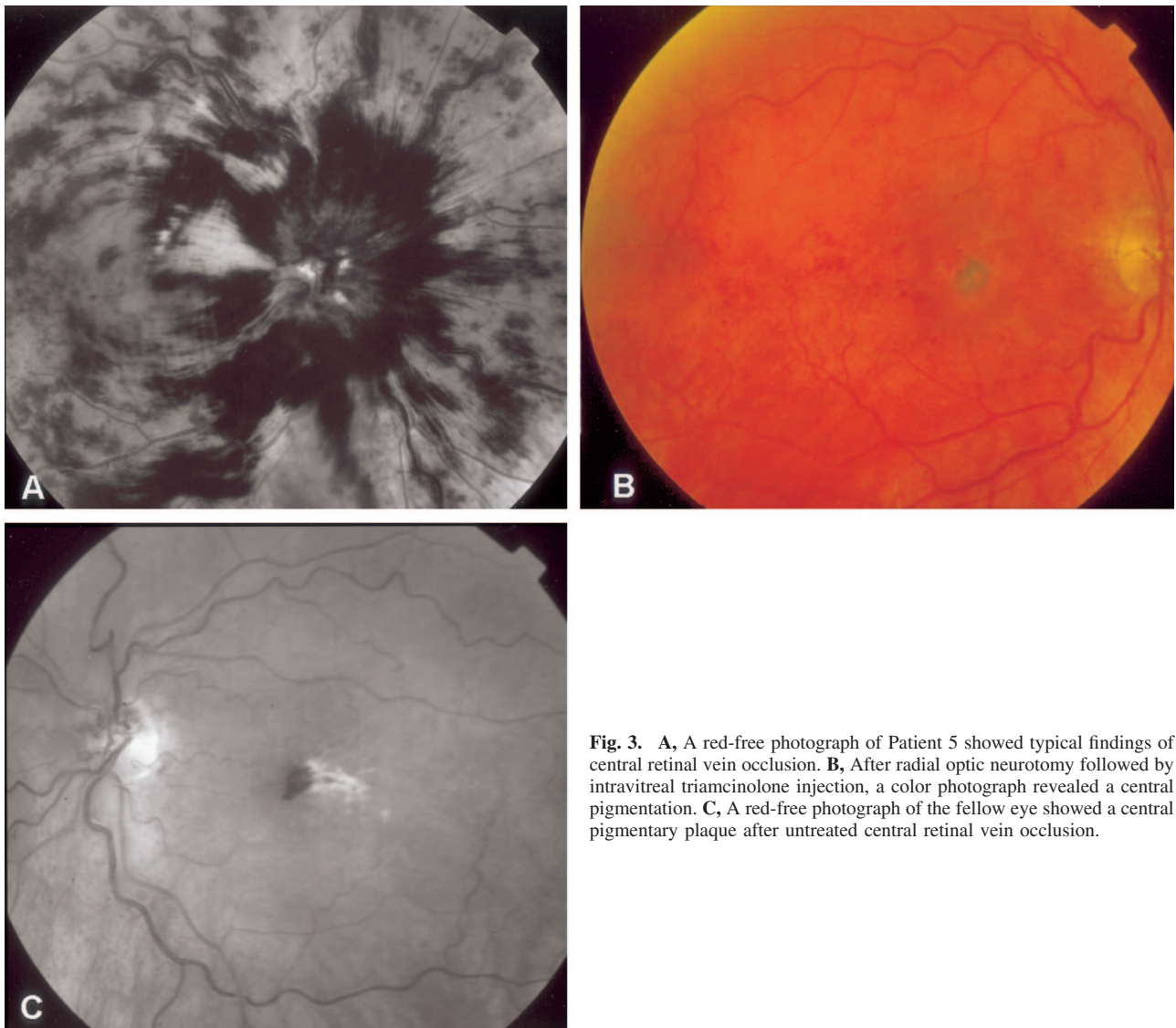
Venooclusive disease can cause retinal edema, serous detachment of the retina, intra- and subretinal hemorrhages, decreased perfusion, and areas of capillary shutdown. Patients described in this report had a number of these parameters, including neurosensory detachment that responded to treatment. After prior intervention (RON in five cases, and panretinal laser treatment in one case), all patients had improvement in caliber of the retinal vessels and resolution of intraretinal hemorrhages, but there was persistence of



**Fig. 1.** This patient underwent radial optic neurotomy due to central retinal vein occlusion. **A**, The color photograph showed remaining intraretinal hemorrhages and macular edema. **B**, Three weeks after intravitreal triamcinolone injection, there was some remaining hemorrhage but complete resolution of the macular edema. In the fovea, there is a large pigmented area at the level of the retinal pigment epithelium.



**Fig. 2.** **A**, Optical coherence tomography (OCT) scan of a patient who underwent radial optic neurotomy due to central retinal vein occlusion showed retinal edema of the macula. **B**, After intravitreal triamcinolone injection, the OCT image revealed resolution of the foveal edema. There is thickening of the retinal pigment epithelium at the fovea.



**Fig. 3.** **A**, A red-free photograph of Patient 5 showed typical findings of central retinal vein occlusion. **B**, After radial optic neurotomy followed by intravitreal triamcinolone injection, a color photograph revealed a central pigmentation. **C**, A red-free photograph of the fellow eye showed a central pigmentary plaque after untreated central retinal vein occlusion.



macular edema. At this time, there were no prominent pigmentary RPE changes seen with ophthalmoscopy, fluorescein angiography, or OCT. After intravitreal triamcinolone injection, the exudative detachment and edema of the retina resolved. Visual acuity did not seem to improve as much as the general appearance of their fundus, however. Each patient in this series had an area of pigmentation and thickening at the level of the RPE in the central macula after rapid resolution of the subretinal fluid.

The cause of the increased pigmentation is not known, but application of known physiologic principles may allow the generation of a hypothesis. Each patient had neurosensory detachment, a common finding in patients with venoocclusive disease.<sup>3</sup> The subretinal fluid could be expected to contain proteins, lipoproteins, and blood breakdown products secondary to the widespread vascular compromise including increased permeability and hemorrhage from the severe CRVO.<sup>3</sup> With a rapid decrease in the exudation from treatment, the aqueous component of the subretinal fluid would be expected to be absorbed more quickly than protein and blood products, which are removed by different channels.<sup>4,5</sup> As seen in other exudative conditions, subretinal fluid generally accumulates and persists in the submacular space. This would lead to potential loculation of fluid in the submacular space, which would be expected to be concentrated in a number of factors derived from the subretinal fluid. The increased pigmentation in the submacular space may be related to a number of factors, including hyperplasia or hypertrophy of the RPE induced by the presence of this material and phagocytosis of the subretinal fluid with its components by the RPE.

Central pigmentation after untreated CRVO is rare. The fellow eye in Case 5 had a central pigmentary plaque after an untreated CRVO. It is possible that the central pigmentation is not seen more frequently in untreated patients because the exudative manifestations such as edema and subretinal fluid take a long time to resolve spontaneously. This lengthy time might allow the RPE to handle the breakdown material within the subretinal fluid more effectively.

Autofluorescence imaging done in two cases showed that the area of foveal pigmentation was autofluorescent, suggesting the presence of lipofuscin, indicating that the pigmentation may be due, at least in part, to phagocytized material. Proliferation of RPE cells in the subretinal space during detachment is often associated with poor photoreceptor recovery. Although there are many reasons for a permanent decrease in visual acuity in patients after CRVO, RPE dysfunction secondary to unique pathophysiologic events induced as a consequence of treatment may be one of them.

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## CILIORETINAL ARTERY OCCLUSION FOLLOWING LASER IN SITU KERATOMILEUSIS

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This report describes a case of bilateral cilioretinal artery occlusion associated with ischemic optic neuropathy following laser in situ keratomileusis in a patient with a borderline titer of anticardiolipin antibody.

The number of patients undergoing laser in situ keratomileusis (LASIK) is growing rapidly worldwide. The possible effects of LASIK on choroidal and retinal circulation have been controversial. In the study by Luna et al.<sup>1</sup>, transient choroidal circulation abnormalities were reported.

We describe the occurrence of bilateral nonsimultaneous cilioretinal artery occlusion associated with ischemic optic neuropathy after LASIK in a patient with a borderline titer of anticardiolipin antibody. This case report confirms the idea that LASIK may have a deleterious effect on posterior ciliary artery blood flow in susceptible patients.

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The authors have no proprietary interest in any of the materials used in this study.

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### Case Report

Bilateral nonsimultaneous LASIK was carried out for correction of high-level myopia in a 26-year-old woman. Preoperative refraction of the right eye was  $-10.00$  sph, and that of the left eye was  $-9.00$  sph. Before LASIK, the best-corrected visual acuity was 20/30 in the right eye and 20/25 in the left eye. Ophthalmoscopy showed that media was clear and the disk was pink with a sharp margin in each eye. Myopic degeneration was present in the posterior pole, leading to a decreased foveal reflex. Examination of the retinal periphery revealed marked peripheral cystoid degeneration and areas of white without pressure. The retinal vessels were normal. The intraocular pressure was 14 mmHg in each eye.

LASIK was performed on the right eye by one of the authors (M.A.J.) on January 12, 2000, followed by the same procedure on the left eye 1 week later on January 19, 2000. During the LASIK procedure, suction was applied for 20 seconds on each eye. The patient noticed sudden loss of vision in her right eye on January 20, 2000. The best-corrected visual acuity in the right eye was 20/400, and a relative afferent pupillary defect was present in the right eye. Funduscopy of the right eye showed cloudy swelling of the retina superior to the macula (Figure 1). A diagnosis of cilioretinal artery occlusion was made. Fluorescein angiography demonstrated that the capillaries of the optic nerve head had filled irregularly, and the cilioretinal artery showed delayed filling. The choroidal filling was also patchy and slow in the posterior pole. Hyperfluorescence of the disk surface was apparent in the late phase (Figures 2A–2C). Results of fluorescein angiography of the left eye were normal at that time.

One week after LASIK on the left eye, the patient had decreased vision in her left eye. The best-corrected visual acuity in the left eye was 20/120. No afferent pupillary defect could be detected. Ophthalmoscopy of the left eye revealed a white patch adjacent to the temporal border of the disk. Fluorescein angiography showed a delay in filling of the cilioretinal artery. Late leakage from the disk surface was present (Figures 3A–3C).

Determination of the complete blood cell count showed a hemoglobin level of 11.8 g/dL (normal range, 12–16 g/dL), hematocrit of 35% (normal range, 36–46%), mean corpuscular volume of 81.2 fL (normal range, 83–97 fL), mean corpuscular hemoglobin of 27.4 pg/cell (normal range, 26–32 pg/cell), and mean corpuscular hemoglobin concentration of 33.7 g/dL (normal range, 32–36 g/dL). The morphology of erythrocytes was reported to be unremarkable. The leukocyte count was  $5,400/\text{mm}^3$  with normal differentiation. The erythrocyte sedimentation rate was 10 mm/hour in the first hour. The platelet count was  $308,000/\text{mm}^3$ . Other laboratory tests disclosed the following values: fasting blood sugar, 89 mg/dL; serum cholesterol, 130 mg/dL (normal range, 130–230 mg/dL); triglyceride, 131 mg/dL (normal range, 50–190 mg/dL); low-density lipoprotein:high-density lipoprotein, 1.3 (low risk for atherosclerosis); serum creatinine, 0.6 mg/dL; prothrombin time, 12.00 seconds (control, 12.00 seconds; percent prothrombin time, 100%; international normalized ratio, 1.0); activated partial thromboplastin time, 38 seconds (normal range, 30–40 seconds); protein C activity, 90% (reference range, 70–130%); and protein S activity, 95% (reference range, 65–140%). Lupus erythematosus cells were not seen. Antinuclear antibody was negative, and rapid plasma reagin was nonreactive. The serum homocystine level was 8  $\mu\text{mol/L}$  (normal range, 4–14  $\mu\text{mol/L}$ ). The results of laboratory assays for factor V Leiden and methylenetetrahydrofolate reductase mutations were negative. Complements C3c and C4 were within normal ranges. The titer of anticardiolipin IgG (determined by enzyme-linked immunosorbent assay) was 0.95; it was considered to be equivocal (negative,  $<0.9$ ; equivocal, 0.9–1.1; positive,  $>1.1$ ). There was no history of fetal loss or any thrombotic event.

Visual acuity of both eyes improved gradually. At the last



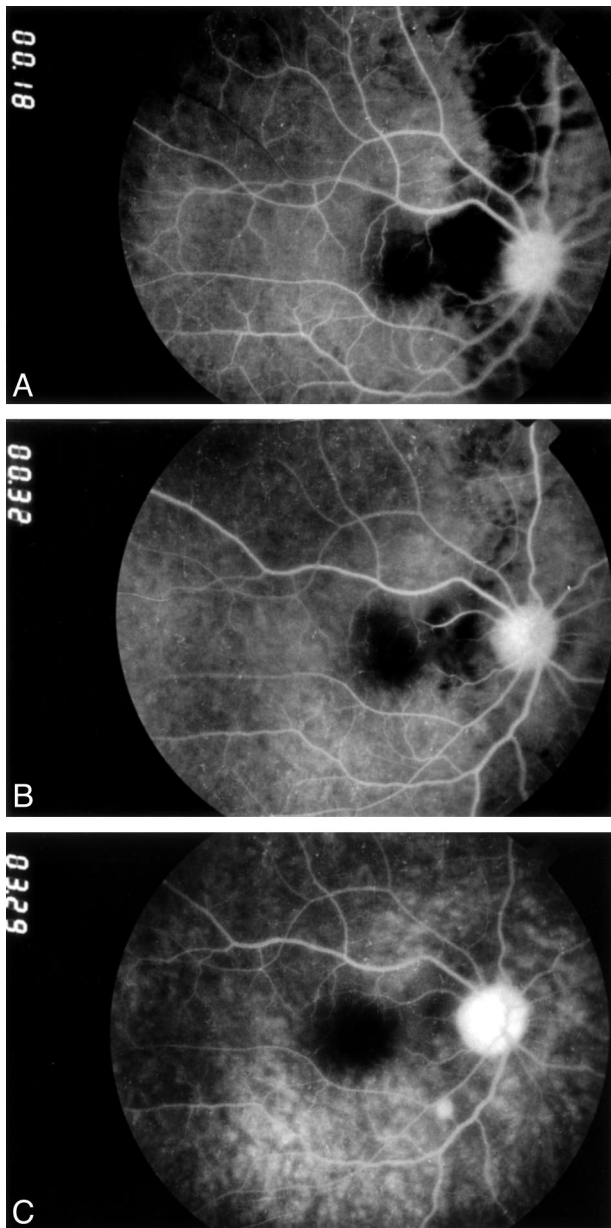
**Fig. 1.** Cloudy swelling of the retina due to cilioretinal artery occlusion in the right eye.

follow-up examination that was performed 30 months later, the best-corrected visual acuity was 20/40 in the right eye and 20/30 in the left eye. The ophthalmoscopic findings included pallor of the disk, narrowing of arteries, and pigmentary changes of the macula in both eyes, which were more apparent in the right eye. Visual field examination revealed moderate generalized depression and a localized defect—cecocentral scotoma—in the right eye (Figure 4) and mild generalized depression associated with a paracentral scotoma in the left eye. The titer of anticardiolipin antibody was checked again and reported to be 1.2 (positive,  $>1.10$ ). However, the titer of antiphospholipid antibody was 2 IU/mL (negative,  $<5$ ).

### Discussion

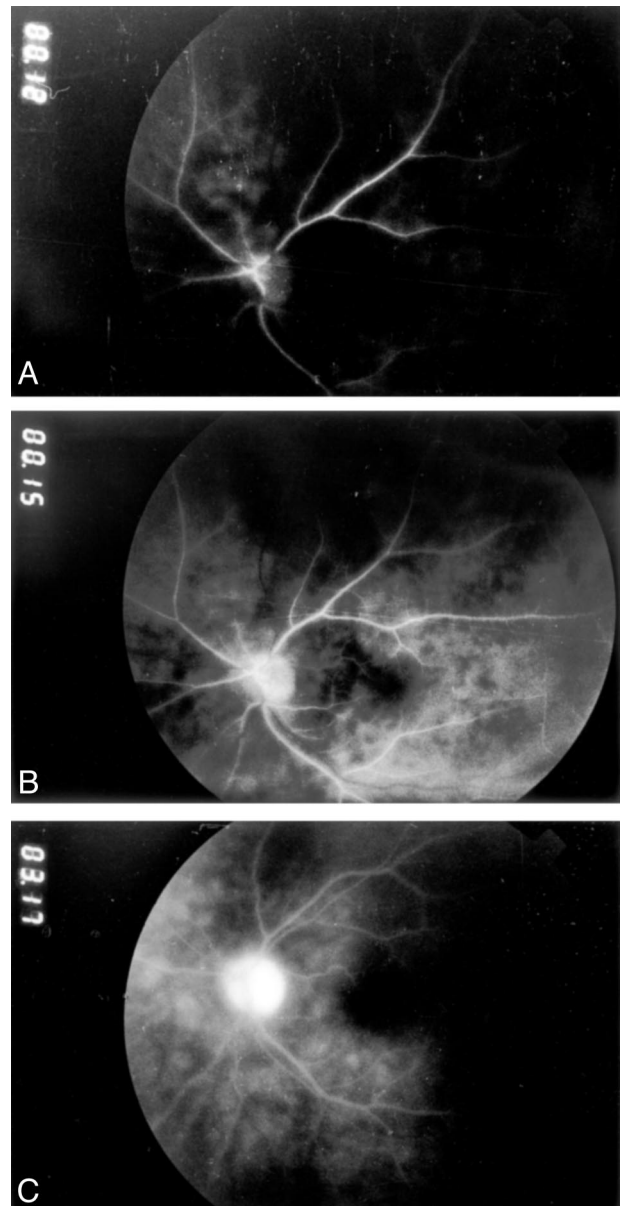
In the human eye, blood flow through the retina is autoregulated.<sup>2</sup> For the choroid, however, the situation is quite different. There is lack of autoregulation of choroidal blood flow, and moderate increments in intraocular pressure cause concomitant reductions in choroidal blood flow.<sup>2</sup> The arterial pressure is on average 7 mmHg lower in the choroidal and posterior ciliary artery circulation than in the central retinal artery circulation.<sup>2</sup>

Cilioretinal artery obstructions fall into three distinct groups: isolated cilioretinal artery obstructions; cilioretinal artery obstruction associated with a central retinal vein occlusion; and cilioretinal artery obstruction in conjunction with ischemic optic neuropathy.<sup>3</sup> In this case, obstruction of the cilioretinal artery occurs in association with ischemic optic neuropathy. Fluorescein angiography findings show that there is stopped or extremely sluggish blood flow in the cilioretinal artery and no focal area of arterial obstruction such as an embolus, as in cases of cilioretinal artery occlusion in young adults with central retinal vein occlusion that were reported by Schatz et al.<sup>4</sup> In their series, obstruction of the cilioretinal artery was attributed to resistance to perfusion of a cilioretinal artery into the retinal capillary bed after the occur-



**Fig. 2.** A–C, Fluorescein angiograms of the right eye. Delayed filling of the cilioretinal artery, slow and patchy filling of the choriocapillaris in posterior pole, and late hyperfluorescence of the disk surface occurred.

rence of central retinal vein occlusion. This was explained by the fact that the perfusion pressure of the posterior ciliary artery circulation, which controls the perfusion pressure of the cilioretinal artery, is lower than the perfusion pressure of the central retinal artery. In our patient, however, obstruction of the cilioretinal artery was probably due to disturbed blood flow in ciliary arteries and seemed to be in conjunction with an ischemic optic neuropathy. Delayed filling of the choriocapillaris involving the posterior pole was



**Fig. 3.** A–C, Fluorescein angiograms of the left eye. Delayed and patchy choroidal filling, delayed cilioretinal artery filling, and hyperfluorescence of the disk occurred.

also revealed by fluorescein angiography. Leakage from the disk surface in the acute phase of the disease and the subsequent optic atrophy with related field defects confirmed the association of ischemic optic neuropathy with cilioretinal artery occlusion.

Antiphospholipid antibody syndromes are hypercoagulable states that occur in patients with antibodies to phospholipids such as anticardiolipin antibodies. Ocular vascular occlusive disease involving retinal and choroidal vessels has been described in patients with primary antiphospholipid syndrome.<sup>5</sup> In a study on 21 patients younger than 40 years who had retinal artery





(usually up to 10 days) between the bleeding and the onset of visual loss. This investigator presumed that this interval was seen because acute blood loss caused an increase in release of endogenous vasoconstrictor agents due to activation of the sympathoadrenergic system and vasomotor center. The absence of the blood–optic nerve head barrier allowed these agents to leak into the optic nerve head tissue and to produce vasoconstriction of the peripapillary choroidal arteries. Failure of autoregulation of blood flow secondary to the decrease in the perfusion pressure below the critical level also had an important role. The perfusion pressure decreased considerably due to a decrease in the systemic blood pressure in the cases reported by Hayreh<sup>7</sup> and secondary to a dramatic increase in the intraocular pressure during LASIK in our patient.

**Key words:** cilioretinal artery occlusion, ischemic optic neuropathy, complications of laser in situ keratomileusis.

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