Calcium Precipitation on the Optical Surfaces of a Foldable Intraocular Lens: A Clinicopathological Correlation

An intraocular lens (IOL) (Hydroview; Bausch & Lomb, Rochester, NY) developed late postoperative opacification of its optical surface, causing significant visual symptoms that required explantation. The lens was processed in our laboratory, and the lens optic, composed of a hydrophilic acrylic polymer, was stained with alizarin red and the von Kossa stain for calcium. The lens also underwent scanning electron microscopy and energy dispersive x-ray spectroscopy of its anterior optical surface. These analyses revealed that the opacity was caused by deposition of calcium phosphate on the lens surface. This process appeared to be dystrophic calcification of unknown cause.

Recent reports of IOL calcification have raised concerns regarding the long-term biocompatibility of 2 modern hydrophilic acrylic foldable lenses: the Bausch & Lomb Hydroview IOL and the Medical Developmental Research (Clearwater, Fla) SC60B-OUV.1-3 In this study, we describe the typical appearance of late postoperative opacification of the former lens with pathological confirmation of IOL calcification.

Report of a Case. An 80-year-old man underwent uneventful phacoemulsification of the left eye and capsular bag fixation of a Hydroview IOL model H60M by one of us (J.P.G.). The patient had a history of rheumatoid arthritis and type 2 diabetes mellitus. The IOL was implanted in the capsular bag under viscoelastics (Viscoat; Alcon Surgical, Fort Worth, Tex). The intraoperative irrigating solution used was balanced salt solution with adrenaline (1:1000). Subconjunctival injections of gentamicin sulfate and betamethasone sodium phosphate were performed at the end of the procedure. Postoperatively, tobramycin and prednisone ophthalmic drops were tapered over 4 weeks. The best-corrected visual acuity 1 month postoperatively was 20/30 OS.

The patient noted a marked loss of vision associated with intense glare 16 months postoperatively. The best-corrected visual acuity was reduced to light perception. Slitlamp examination of the anterior segment revealed a dusty haze or granularity present on the optical surfaces of the lens (Figure 1). Evaluation of the posterior segment was not possible because of hazy media secondary to IOL opacification. As attempts to clear the optical surfaces of the IOL with the Nd:YAG laser were not successful, the IOL was explanted 20 months postoperatively. It was freed from the surrounding capsule by viscodissection and then removed through a 6.0-mm sclerocorneal tunnel. A rigid polymethyl-methacrylate IOL model P 359 (Bausch & Lomb) was placed in the capsular bag. Incisional biopsies of conjunctiva and iris were performed during IOL removal and exchange to rule out the presence of dystrophic calcification in those tissues. The patient’s visual acuity improved to 20/400 with absence of glare immediately after the IOL exchange. Evaluation of the posterior segment at this stage revealed presence of severe nonproliferative diabetic retinopathy. However, the best-corrected visual acuity decreased to light perception after 2 months’ follow-up because of the worsening of the diabetic retinopathy/maculopathy, which was further investigated and treated in consultation with a retina specialist.

Gross and microscopic analyses of the explanted IOL were performed, and photographs were taken to document the findings. The IOL was then bisected for histochemical and scanning electron microscopic evaluation. For histochemical analysis, one half of the IOL was rinsed in distilled water, immersed in a 1% alizarin red solution for 2 minutes, rinsed again in distilled water, and reexamined under the light microscope. A slice of the optic of the Hydroview IOL was performed, the resultant cylindrical block was dehydrated and embedded in par-

Figure 1. Slitlamp photograph of an implanted Hydroview intraocular lens (Bausch & Lomb, Rochester, NY) with a granularity present on the optic.
affin, and sagittal sections were performed. Special stains included the von Kossa stain for calcium.4,5 The other half of the lens optic was air-dried at room temperature for 7 days, sputter-coated with aluminum, and examined under a 2500 Delta scanning electron microscope (Nissei Sangyo America, Schaumburg, Ill) equipped with a Kevex (Scotts Valley, Calif) x-ray detector. The conjunctival and iris tissue were also prepared for histological/histochemical examination and stained with the alizarin red/light green and von Kossa methods.

Pathologic Findings. Gross evaluation revealed that the optical surfaces of the unstained IOL were covered by a layer of irregular granular deposits. The deposits occurred on both anterior and posterior optical surfaces, but not on the haptics (Figure 2). They stained positive with alizarin red (Figure 3). Sagittal sections of the optic of the IOL stained using the von Kossa method were positive, showing a continuous layer of dark brown, irregular granules on all surfaces (anterior, posterior, and edges) of the lens (Figure 4). Scanning electron microscopic analysis of the optic’s anterior surface revealed granular deposits composed of multiple spherical-ovoid structures (Figure 5). Energy dispersive x-ray spectroscopy performed on the surface shown in Figure 5 revealed a high peak for calcium and a lesser peak for phosphate.
Histochemical evaluation of the conjunctival and iris biopsy specimens, using alizarin red stain and von Kossa silver stain, did not reveal any evidence of calcium salts (Figure 7).

Comment. We have recently reported on the lens described here, the Bausch & Lomb Hydroview, as well as another hydrophilic IOL, the Medical Developmental Research SC60B-OUV. With both lens designs, the opacification appears to be related in part to calcium deposition on the external optical surfaces (in the case of the Hydroview) or within the IOL optic (in the case of the SC60B-OUV). Our first publication on calcification of the Hydroview design reported on 1 explant from Australia and 4 explants from Sweden. This is the first report of calcification of Hydroview lenses observed in Canada. As in the previous cases, the dystrophic calcification was limited to the external optical surfaces of the lens. In the case reported here, the absence of dystrophic calcification in ocular anatomical structures of the patient, such as conjunctiva and iris, was confirmed histopathologically. More than 400,000 Hydroview lenses have been implanted in >400 centers worldwide. We are aware of 272 similar cases of late postoperative opacification, from which 83 lenses were explanted because of significant visual impairment. These reports have been clustered in 29 centers, including Hong Kong, Canada, Sweden, Germany, and Australia, among others. One of us (J.P.G.) has explanted several Hydroview IOLs for similar reasons. Although the composition of the deposits has been determined to be hydroxyapatite, the pathogenesis of this complication is still obscure. Awareness of this condition is warranted as Nd:YAG laser treatment does not seem to be helpful in removing the deposits from the lens surfaces and possibly damages the surrounding capsule, compromising in-the-bag fixation of a new IOL after explantation of the opacified lens.

Suresh K. Pandey, MD
Liliana Werner, MD, PhD
David J. Apple, MD
Charleston, SC
Jean-Pierre Gravel, MD
Quebec City, Quebec

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Corresponding author and reprints: Liliana Werner, MD, PhD, Department of Ophthalmology, Storm Eye Institute, Medical University of South Carolina, 167 Ashley Ave, PO Box 250676, Charleston, SC 29425-5336 (e-mail: wernerl@musc.edu).


Choroidal Melanoma Treated With Cryotherapy

The treatment of small choroidal melanocytic tumors is evolving because of the recognition of risk factors for growth and metastasis. Ideally, the treatment of small melanocytic tumors would completely eradicate the tumor without compromising visual acuity. Cryotherapy has been used in a limited fashion for the treatment of choroidal melanomas. Lincoff et al4 and Browkina et al5 evaluated cryotherapy in small series of patients with medium-sized and large melanomas, but exudative retinal detachment and incomplete tumor destruction compromised treatment. We report the clinical and histopathologic findings in a patient treated with cryotherapy for a small, growing choroidal melanocytic tumor 125 months before death from unrelated causes.

Report of a Case. The patient was initially seen in August 1988 for a routine eye examination and was found to have a pigmented juxtapapillary choroidal lesion (Figure 1). By Janu-
ary 24, 1989, the lesion had clearly enlarged. Examination at that time showed visual acuity of 20/20 and a normal anterior segment. A pigmented juxtapapillary lesion was located inferonasal and adjacent to the optic nerve (Figure 2). Echography demonstrated that the tumor measured 1.8 mm in thickness, 7.5 mm in longitudinal diameter, and 6.0 mm in transverse diameter. The patient was enrolled in a trial of cryotherapy for treatment of small choroidal melanocytic tumors, and the tumor was treated on March 15, 1989, using a double freeze-thaw cryotherapy with a conventional retinal cryoprobe. The optic nerve was included in the treatment. On the first postoperative day, the patient’s vision was no light perception. The tumor diminished in thickness, but a small area of pigmentation remained in the center of the treatment scar. This area of pigmentation was treated again on August 10, 1993. The tumor regressed to a flat chorioretinal scar after the second cryotherapy treatment. Periodic liver function tests and chest x-ray films were obtained and indicated no suggestion of metastatic disease. There was no clinical evidence of recurrence of the tumor (Figure 3). The patient died of cardiovascular disease 125 months after his initial treatment. No autopsy was performed, but the eyes were obtained for histopathologic study.

The left globe was fixed in 10% neutral buffered formalin and processed for light microscopy. Serial sections were prepared through the entire extent of the chorioretinal scar and studied for evidence of residual tumor. Microscopic examination showed near full-thickness atrophy of the retina and choroid in the area of the cryotherapy (Figure 4). The retina in the area of cryotherapy consisted of a thin layer of glial cells with some migration of hyperplastic retinal pigment epithelium into the
retina (Figure 5). There was a thin monolayer of cells on the surface of the retina (epiretinal membrane). A few large vessels were present in the choroid, but there was atrophy of the small and medium-sized choroidal blood vessels. Occasional pigment-containing macrophages were found within the choroid, but no tumor cells were present, and no tumor cells were evident in the sclera or retina.

The optic nerve was atrophic, and loss of axons and myelin and thickening of the pial septae were evident (Figure 6). The sclera in the area of cryotherapy was of normal thickness (Figure 7).

Comment. The results of our histopathologic study of this case are consistent with complete destruction of this small, growing choroidal melanoma by freezing. Careful study of serial sections failed to disclose any remaining tumor cells. Hidayat et al have reported the mechanism of cellular injury in rapid freezing of uveal melanomas to be plasmalemmal breaks, dissolution of cytoplasmic matrix, and damage to cellular organelles, suggesting a lethal effect on melanoma cells. Similar mechanisms of cell injury were undoubtedly responsible for the damage evident to the optic nerve and the retina overlying the tumor.

Exudative complications of cryotherapy that have been observed in the treatment of medium-sized and large melanomas were not found in this case. The lack of these complications may be due to the smaller size of the tumor and to the sequential application of less intense cryotherapy than was used in the earlier studies. Also, no apparent damage to the sclera occurred as a result of the cryotherapy.

The complete tumor destruction seen in this case indicates that cryotherapy may be useful as a primary treatment for small, growing choroidal melanomas or as an adjunct for treating recurrences of melanomas treated primarily with radioactive plaque.

David J. Wilson, MD
Michael L. Klein, MD
Portland, Ore

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Corresponding author and reprints: David J. Wilson, MD, Casey Eye Institute, Oregon Health & Science University, 3375 SW Terwilliger Blvd, Portland, OR 97201-4197 (e-mail: wilsoda@ohsu.edu).


The World Trade Center Disaster: A Brief On-site Report From Ground Zero

In the aftermath of the September 11, 2001, World Trade Center tragedy, the American Academy of Ophthalmology informed us of the need for ophthalmologists to treat the myriad eye complaints that ensued when the twin towers became a noxious cloud of dry wall, gypsum, cement, marble, asbestos, steel, and glass, released from the impact of the 2 commercial airliners hijacked by terrorists. Many ophthalmologists in the New York City area heeded this call and volunteered to provide care at “ground zero.” It was a unique experience that we would like to share with the ophthalmologic community. We worked primarily in a makeshift triage center at Stuyve-
sant High School on Chambers Street, which was the closest clinic to ground zero. From that triage/command center, we dealt with rescue workers from the Fire Department, City of New York, and the New York State Emergency Medical Services, city officials, various construction crews, and other volunteers. We worked as part of the ophthalmology team at this site and attended to various eye injuries. This center was set up for survivors of the tragedy, but because so few survived, it became more of a support center for the disaster relief team. We believe our observations may be helpful to others who are creating contingency plans to deal with such disasters.

The leading ophthalmologic symptoms we encountered were painful, burning eyes secondary to debris, corneal abrasions, and keratitis caused by exposure to smoke and chemical fumes. Diagnosis was aided by using proparacaine hydrochloride, fluorescein sodium ophthalmic strips, and direct ophthalmic examination. The most common treatment was irrigation with 0.9% isotonic sodium chloride solution. In the triage center, a bench with standing poles for bags of isotonic sodium chloride solution given intravenously was used for the numerous patients who came in for eye irrigation. Almost all of those treated went back to the site again in a few hours.

New York City, with arguably one of the most responsive emergency medical services in the country, was incredibly taxed by this apocalyptic disaster. It seemed very clear that any city would be ill-prepared to deal with a tragedy such as this. Starting with the main “command” center, there was some degree of disorganization. There was no strong chain of command, especially at the volunteer level. Probably, the deaths of the top leaders of the emergency and occupational/environmental medical services and the fire department in the twin towers’ collapse also contributed to this problem. The most efficient part of the rescue effort at the center was dispensing food and water for the rescue. There were ample medical supplies, although their distribution was not optimal. Distribution of these supplies could have been better supervised.

Most of the rescue workers did not use safety goggles, which could have prevented many of the eye injuries. The most common reasons for not using them were that the workers did not know where to obtain safety goggles or that the visor fogged too easily and impeded vision. A few said the eye shields were too cumbersome. Virtually all agreed that availability of more showers close to the site would have been valuable.

After discussion with patients and colleagues, we have some recommendations to improve the medical care in such emergencies.

1. There should be an existing chain of command in the medical corps, and identification badges should be issued for persons who had previously volunteered to assist in such emergency efforts. We found people who were unauthorized inside the triage center. Because of the lag time for the arrival of military medical corps, some level of security is needed for the civilian medical volunteers tending to the injured.
2. Respirators and goggles should be available to all the workers at the trauma site. Despite the fact that an ample supply was present, no assigned personnel were present or reachable to distribute the gear to individuals who would most need them, especially the workers at ground zero who were working under the cloud of noxious fumes.
3. There should be easy availability of mobile showers near the site. If no available water lines are open, bags of isotonic sodium chloride solution or gravity-dependent portable showers can be quickly mobilized to the site.
4. There should be an efficient distribution of medical supplies.
5. Protective goggles that are light and not cumbersome should be available to the rescue crew. A briefing on the use of eye protection to educate the rescue workers is important.
6. The medical team chiefs of each specialty present should have telephones or some mode of communication. In addition, a redundant line of communication should be in place (ie, a short-hand radio if a cellular phone or landline communication is not possible). Assistants who are responsible for scheduling volunteer shifts, physician assignments, and general organization of medical staff and supplies should be on site.
7. Finally, good communication is needed from the feeder staging areas, such as the Javits Convention Center, to the triage centers at the disaster site, communicating the need for required personnel and supplies at ground zero. For example, the command center at the Javits Convention Center was not fully aware that there was a need for certain specialists, such as ophthalmologists and nurses, despite the presence of ample volunteers for these positions.

Overall, our experience was entirely positive. The shortcomings were overcome by the sheer power of team effort. It was an occasion we hope we never see again. No one can be prepared for such a tragedy, but in the spirit of New York City, and ultimately, of the American people, demonstrated that any challenge can and will be overcome by the many brave men and women who risked their lives for the preservation of human life. In such calamities, some previous planning will help preserve the sight of those emergency workers who rush to the scene.

Shree K. Kurup, MD
Emerson T. Que, MD
Danny H. Kaufmann Jokl, MD
Valhalla, NY

Corresponding author and reprints: Emerson T. Que, MD, Department of Ophthalmology, New York Medical College, Westchester Medical Center, Valhalla, NY 10595.
Elschnig Pearls on the Posterior Capsule in a Pseudophakic Eye

Posterior capsule opacification (PCO) following cataract surgery is the manifestation of the migration and proliferation of lens epithelial cells on the posterior capsule. When PCO encroaches onto the visual axis, it causes light scatter and deterioration of vision. This condition is usually treated by a posterior capsulotomy with a Nd:YAG laser. There is a rare case, however, of a patient who had spontaneous regression of PCO from Elschnig pearl proliferation, with improvement of visual acuity.1 We report a similar case of spontaneous Elschnig pearl regression taking place throughout 3 years.

Report of a Case. In November 1997, a 75-year-old man visited us with blurred vision in his right eye, 3 years after cataract surgery. Cataract surgery was performed by a local physician in 1994, and the details of the operation were unknown. He had been treated with oral medication for hypertension and arrhythmia. Other medical history was unremarkable.

On examination, a single-piece polymethylmethacrylate intraocular lens (IOL) was seen in the posterior chamber and was associated with marked Elschnig pearls reaching the central region of the posterior capsule (Figure, A). Seemingly, the surgery had been performed using phacoemulsification with a “can opener” capsulotomy. The site of IOL implantation (inside or outside of the bag) could not be confirmed. No apparent operative complications were found. Despite the symptom of blurred vision, the patient’s visual acuity was 20/15 OD with −0.75 diopters (D), and thus, a posterior capsulotomy was not performed.

In August 2000, he returned after the interval of 3 years with decreased vision in his left eye that was diagnosed as cataract. Slitlamp examination revealed that Elschnig pearls of the right eye significantly decreased (Figure, B). In particular, those behind the IOL optic disappeared almost completely. The posterior capsule was intact. The patient had not received any surgical, laser, or medical treatments for the right eye since the last visit. Corrected visual acuity was 20/15 with −1.0 D. The patient gave no report of blurred vision in his right eye. There was no pseudophakodonesis.
In October 2000, parts of Elsch
ign pearls showed a swing on eye movements (Figure, C). One month later, this portion disappeared completely (Figure, D).

The fellow left eye underwent phacoemulsification and implantation of a silicone IOL within the capsular bag in August 2000. There was no pseudoexfoliation and phacodensification. Postoperatively, neither development nor regression of PCO has been observed in this eye until now.

Comment. Spontaneous regression of Elschign pearls is very rare.1 This is partly because significant PCO is usually treated by the Nd:YAG laser immediately when recognized. In this case, despite the blurred vision, the corrected visual acuity happened to remain at 20/15 OD, and the patient could manage well with that acuity, allowing for the observation of the long-term natural course.

There has been a reported case of spontaneous improvement in visual acuity after PCO,2 but it was related to the displacement of a dense central area of Elschign pearls by the progressive capsule contraction from fibrosis. Caballero et al3 reported several cases of spontaneous disappearance of Elschign pearls after a Nd:YAG laser capsulotomy. Hollick et al4 demonstrated that lens epithelial cells that migrated onto the posterior capsule in the early postoperative period substantially regressed between 30 and 90 days postoperatively. They attributed this phenomenon to the tight adhesion between the IOL material and capsular bag. This postulate, however, does not apply to the case presented here because there was some space between the IOL optic and the posterior capsule as evidenced by the movement of Elschign pearls (Figure, C). It may be that the lack of tight contact between the IOL and the capsule led to the exposure of Elschign pearls to the aqueous humor, resulting in the drop-off of loosened and inactive cells from the posterior capsule.

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Corresponding author and reprints: Tetsuro Oshika, MD, Department of Ophthalmology, University of Tokyo School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan (e-mail: oshika-thy@umin.ac.jp).


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**Repair of Impending Macular Hole in the Early Postoperative Period as Evaluated by Optical Coherence Tomography**

— Tetsuro Oshika, MD, Fumiaki Yoshitomi, MD, Yasuyuki Nakashima, MD, Tokyo, Japan

High-resolution cross-sectional imaging provided by optical coherence tomography (OCT) facilitates assessment of the postoperative state as well as preoperative vitreoretinal state of idiopathic macular holes. Although the hole is considered to be closed in the first few postoperative days by studies using gas or silicone oil tamponade,1,2 the detailed postoperative change in the fovea in the early postoperative period is unknown because of the poor quality of the image due to the use of gas or silicone oil. Impending macular hole may resolve either from spontaneous vitreous detachment or with vitrectomy with separation of the vitreous cortex from the retina. Herein we describe 2 patients with impending macular hole who underwent vitrectomy without gas tamponade and from whom we were able to obtain a series of good-quality OCT images from before and after surgery, and discuss the repair process of impending macular hole.

**Report of Cases.** Case 1. A 65-year-old woman had a 1-week history of blurred vision in the left eye, with best-corrected visual acuity of 20/60. Contact lens biomicroscopy disclosed foveal changes typical of idiopathic impending macular hole, with a loss of foveal depression and a yellow ring in the fovea. No posterior vitreous detachment was identified on biomicroscopy. Horizontal and vertical cross-sectional images provided by OCT revealed loss of the foveal pit associated with a bridgelike inner retina and hyporeflective cystic formation apparently due to disruption of the outer retinal layer extending to the retinal pigment epithelium. The posterior hyaloid was adherent to the foveal center with perifoveal posterior hyaloid separation (Figure). The fellow eye was normal on biomicroscopy and OCT.

Case 2. A 75-year-old woman noted distorted vision in the left eye 2 weeks before being examined. Her best-corrected visual acuity in this eye was 20/60 due to impending macular hole, the biomicroscopic and OCT findings of which were similar to those in case 1. The fellow eye had developed a full-thickness macular hole (stage 3) and had undergone successful vitrectomy and gas tamponade with hole closure 10 months previously.

**Results.** The 2 patients were informed of the known natural course of idiopathic impending macular hole and its surgical intervention. Each patient consented to vitrectomy with careful peeling of the posterior hyaloid from the center of the fovea. The postoperative course was uncomplicated, and the ocular media remained clear enough to allow a series of sequential OCT evaluations as early as the first postoperative day. The Figure shows preoperative and postoperative cross-sectional OCT images through the fovea in case 1, demonstrating a restoration of foveal configuration. On the first postoperative day, a pronounced decrease of cystic spaces was found with early depression of the central fovea with disappearance of vitreous adhesion to the fovea. Subsequent daily OCT evaluations revealed a further recovery of foveal contour in such a manner that the inner retina appeared slightly thickened and depressed while the
Case 1. Preoperative and postoperative optical coherence tomographic (OCT) images of a 65-year-old woman with impending macular hole. Preoperative OCT shows intrafoveal cyst with disruption of the outer retinal layer and a partially detached posterior hyaloid adherent to the roof of the cyst. On the first postoperative day, both a horizontal and a vertical OCT section showed the roof of the cyst slightly depressed, increasing its thickness. During subsequent days, the foveal depression recovered with reapproximation of the edge of the disrupted outer retinal layer. One week postoperatively, a small residual clear space was identified in the fovea. One month after surgery, the image shows normal foveal configuration.
underlying cysts regressed and appeared to be replaced by outer retinal tissue. By 1 to 2 weeks after surgery, the fovea had a distinct pit with minimal optical clear space under it. The foveal configuration appeared normal 1 month after surgery and remained unchanged when examined at 6-month follow-up. Case 2 also had a foveal restoration with a similar time course. In concert with the anatomical recovery, best-corrected visual acuity in both patients improved to 20/40 at 1 week after surgery and to 20/25 at 6 months.

Comment. The preoperative OCT images of these cases are consistent with impending macular hole characterized by an intraretinal cyst that has raised the foveal floor and disrupted the outer retina probably due to perifoveal posterior vitreous detachment with residual adhesion to the fovea. The natural course of impending macular hole is variable among patients, but surgical intervention may be beneficial to prevent a possible progression to full-thickness macular hole. The patients described herein underwent successful vitrectomy with peeling of the posterior hyaloid without gas injection. With no gas in the eyes, it was possible to obtain good-quality OCT images in the early postoperative period. The findings indicate that impending macular hole begins to resolve as early as the first postoperative day and that an anatomical restoration of the fovea is achieved by about 1 month after surgery.

Recently the natural history of an impending macular hole has been clarified using OCT. According to that report, foveal pseudocysts are the first step in full-thickness macular hole formation, which is the result of incomplete vitreous detachment in the perifoveal area. After the occurrence of a split in the foveal tissue, the outer retinal layer is disrupted in some eyes, and the unroofing of a foveal pseudocyst results in the full-thickness macular hole. Disruption of the outer retinal layer is thought to occur because of the particular anatomy of the central foveal Muller cells.

The OCT images described herein provide additional information for understanding the repair process of idiopathic macular holes. We found 2 anatomical changes occurring in the fovea. First, the roof of the cyst gradually increased in thickness and its separation from the underlying layer diminished (vertical change). The second was reappraisal of the edge of the disrupted outer retinal layers (horizontal change). We measured the thickness of the roof and vertical and horizontal diameter of the cyst in case 1 to see how the fovea changes. The thickness of the roof before the surgery and at postoperative days 1 and 4 measured 60 µm, 88 µm, and 108 µm, respectively. The horizontal diameter of the cyst measured 250 µm, 240 µm, and 180 µm, respectively. These facts indicate that disrupted outer retinal layers begin to reapproach as well as the gradual depression of the roof of the cyst, increasing its thickness following the release of vitreous traction.

In conclusion, detailed observations of impending macular hole after pars plana vitrectomy using OCT have revealed 2 factors: depression of the inner part of the cyst with an increase in thickness and reappraisal of the disrupted outer retinal layer. These changes are associated with resolution of the impending macular hole.

Akinori Uemura, MD
Eisuke Uchino, MD
Norihito Doi, MD
Norio Ohba, MD
Kagoshima-shi, Japan

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Corresponding author: Akinori Uemura, MD, Department of Ophthalmology, Kagoshima City Hospital, 20-17 Kajiya-cho, Kagoshima-shi 892-8580, Japan (e-mail: akbru@ml.kch.kagoshima.kagoshima.jp).


Cryotherapy as a Primary Treatment for Choroidal Melanoma

The treatment of small melanocytic tumors of the uvea is appealing because of the prospect of local destruction of a potentially lethal tumor while it is still confined to the eye. However, enthusiasm for treating small melanocytic tumors of the uvea has been tempered by the lack of an effective local treatment that is free from significant local side effects and by the difficulty in identifying which small uveal melanocytic lesions should be treated. In the past few years, several studies have helped identify which small uveal melanocytic tumors are at particularly high risk for growth and/or metastasis. Identification of high-risk small tumors has prompted reevaluation of the management of these tumors and promoted the development of vision-sparing treatment modalities.

Cryotherapy has been used in a limited fashion for the treatment of uveal melanomas. Lincoff et al3 and Brovkin et al4 evaluated cryotherapy in small series of patients with uveal melanoma. In both series the effectiveness of cryotherapy was limited by exudative retinal detachment and incomplete tumor destruction. However, in both of these trials, medium to large melanomas were treated, and the treatment was designed to destroy the tumor in 1 treatment session. Herein we report a prospective trial of cryotherapy in the treatment of 5 patients with small, growing choroidal melanocytic tumors with the use of multiple treatment sessions to limit the complications of the procedure and to ultimately achieve a flat chorioretinal scar.

Patients, Materials, and Methods. Patients were considered eligible for this trial if (1) they had graphically documented growth of a choroidal lesion with the ophthalmoscopic and echographic features of
a choroidal melanoma (photographically documented growth was defined as an increase in the size of the tumor, relative to retinal landmarks, as determined by comparison of serial color photographs); (2) the thickness of the choroidal tumor measured less than 3.0 mm; and (3) the basal diameter was less than 16 mm. Tumors that extended into the ciliary body were not included in this trial, but peripapillary tumors were eligible. This decision was based on the lack of vision-sparing options for patients with peripapillary choroidal melanomas. No specific minimum diameter or thickness was required as long as the tumor met the above requirement for documented growth. Patients were not included in the trial if they had undergone prior treatment for choroidal melanoma, including irradiation, laser, or surgery. All patients underwent pretreatment and posttreatment examination, color fundus photography, and A- and B-scan echography. Patients were examined at a minimum of 1 day prior to treatment, at the time of treatment, 1 day posttreatment, 7 to 14 days posttreatment, 3 months posttreatment, and then at 6-month intervals. Other visits were permitted at the discretion of the treating ophthalmologist. Visual acuities were recorded using a projected visual acuity system but were not standardized.

The tumors were treated with a double freeze-thaw method that uses a conventional retinal cryoprobe. The end point of each freeze was whitening of the surface of the tumor. Applications with the cryoprobe were placed in an overlapping fashion so that the entire tumor was treated. One patient (patient 3) with a peripapillary tumor was treated with an endocryoprobe to try to limit the damage to the optic nerve. Patients were re-treated at 4- to 6-week intervals until a flat choriotinal lesion, as determined by ophthalmoscopy and echography, was present. The protocol was approved by the Oregon Health Sciences University Institutional Review Board for enrollment of 8 patients. Five patients were enrolled in the trial between 1989 and 1999, at which point recruitment was closed.

Results. The pretreatment and posttreatment clinical features of the tumors are summarized in the Table. Pretreatment and posttreatment fundus photographs are shown in the Figure. Treatment of all the tumors resulted in the desired clinical end point of a flat chorioretinal scar. This appearance was maintained throughout the follow-up period. The number of treatments required to achieve this end point varied from 2 to 5. In patients 4 and 5 there is a small central area of increased pigmentation (Figure H-J), but these areas are completely flat and have not shown an increase in size over the follow-up period.

Notable complications of the treatment included a visual acuity of no light perception in 1 patient (patient 1). This patient had a peripapillary tumor, and optic nerve damage resulted from direct cryoinjury to the optic nerve at the time of treatment. Loss of vision occurred immediately following cryotherapy and there was no recovery of vision following the injury. Patient 2 has age-related macular degeneration and developed a subfoveal neovascular membrane that is thought to be unrelated to the cryotherapy. Patient 3 developed a branch retinal vein occlusion that did not significantly affect her vision. Patient 5 developed a transient exudative retinal detachment and an epiretinal membrane with a reduction in visual acuity from 20/20 to 20/30.

Patient 1 died from renal and cardiovascular disease 125 months after treatment of his intraocular tumor. There was no clinical evidence of metastatic disease. An autopsy was not performed. Patients 2 through 5 are alive without clinical evidence of metastatic disease. The mean follow-up in the 5 patients is 65 months, with a range of 16 to 125 months.

Comment. Treatment of small, growing melanocytic tumors remains a controversial topic. Risk factors for growth of small melanocytic tumors have been reported in 2 studies. Shields et al1 found that greater initial tumor thickness, posterior margin of the tumor touching the optic nerve, symptoms of flashes and floaters, orange pigment on the surface of the tumor, and subretinal fluid predicted growth. The Collaborative Ocular Melanoma Study group found that factors predictive of the growth of small melanomas were a greater initial diameter or thickness, presence of orange pigment on the surface of the tumor, the absence of drusen, and the absence of retinal pigment epithelium changes at the margin of the tumor.2 Risk factors for metastasis of small choroidal melanomas have been reported as posterior margin of the tumor touching the optic nervehead, documented growth, and greater initial tumor thickness.3 Only small, growing melanomas were treated in this trial.
Cryotherapy has received little attention as a means of destroying uveal melanomas. Theoretically, this method has several potential advantages: (1) melanin-containing cells are sensitive to destruction by freezing; (2) cryotherapy is an accepted method of treating melanomas elsewhere, including the conjunctiva; (3) cryotherapy has been used for more than 20 years in treating retinal diseases, including vascular tumors, retinoblastoma, retinal tears, and retinal detachment; (4) when using cryotherapy, the approach is from the choroid; thus, in addition to a direct effect on the tumor cells, cryotherapy can have an additional effect of compromising the tumor’s blood supply; and (5) transscleral treatment also results in treatment of intrascleral tumor cells.

The acute effects of cryotherapy on uveal melanomas has been studied by Hidayat et al. These authors found that following rapid freezing there were ultrastructural changes that included plasmalemmal breaks, dissolution of cytoplasmic matrix, and damage to cellular organelles all of which suggest a lethal effect on melanoma cells. These authors also studied one melanoma that was treated with rapid freezing 6 months prior to enucleation. The tumor was incompletely treated, but in the area of cryotherapy, there was extensive necrosis of tumor cells and infiltration with melanophages.

A substantial number of complications occurred in our small patient population. External cryotherapy to a peripapillary tumor resulted in a visual acuity of no light perception due to cryoinjury to the optic nerve. This complication was later avoided by using an endocryoprobe to successfully treat a second peripapillary tumor. Less severe complications included branch retinal vein occlusion, transient exudative retinal detachment, and epiretinal membrane formation. Despite these complications, 4 of the 5 patients maintained good visual acuity after cryodestruction of the tumor (1 subsequently lost vision in the treated eye owing to age-related macular degeneration).

Other options for treating small, growing melanomas include radiation therapy or transpupillary thermotherapy (TTT). Radiation therapy of small tumors carries with it a high likelihood of loss of central vision if...
the optic nerve or fovea receives a radiation dosage in excess of 3000 to 4000 rads equivalents.

What role cryotherapy and TTT will have in the treatment of small choroidal melanomas is not known. Both treatments require multiple treatment sessions to limit complications. Transpupillary thermotherapy has the advantage of not requiring conjunctival incisions and having a more discrete border between treated and untreated areas. Cryotherapy has the advantage of a visual end point to each treatment session. Unlike TTT, cryotherapy is a transscleral treatment and should result in treatment of the intraocular tumor in the area of cryotherapy. Certain tumor characteristics may be a relative indication for one type of treatment, eg, tumor pigmentation and location. More peripheral tumors may be easier to treat with cryotherapy while posterior tumors may be easier to treat with TTT. Transsclular thermotherapy appears at this time to be more effective in more pigmented tumors, so lack of pigmentation may be a relative indication for cryotherapy. Finally, the 2 treatments are not mutually exclusive and may find utility in combination with each other, or with irradiation. Both treatments could find utility in the treatment of marginal recurrences of initially irradiated tumors. Whether either TTT or cryotherapy will result in permanent tumor eradication requires further follow-up of treated patients. The mean follow-up in this trial was 65 months, but given the small size of the tumors and the slow growth of uveal melanomas, additional time is necessary to be certain late recurrences will not develop.

In conclusion, we have used cryotherapy to treat 5 patients with small, growing melanocytic tumors. All tumors were treated to an end point of a flat chorioretinal scar and maintained this end point over the follow-up period. Using multiple treatment sessions, we were able to avoid the incomplete tumor destruction and intraocular morbidity reported in earlier trials about the cryodestruction of choroidal melanomas.

David J. Wilson, MD
Michael L. Klein, MD
Portland, Ore

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Corresponding author: David J. Wilson, MD, Casey Eye Institute, Oregon Health Sciences University, 3375 SW Terwilliger Blvd, Portland, OR 97201 (e-mail: wilsonda@ohsu.edu).