Hydroxyapatite Formation on Implanted Hydrogel Intraocular Lenses

Three Chinese patients undergoing implantation with the same hydrogel intraocular lens (IOL) (Hydroview; Bausch & Lomb Surgical, Claremont, Calif) developed delayed IOL opacification with unusual clinical features. The IOLs were made from a 2-hydroxyethylmethacrylate/6-hydroxyhexylmethacrylate (HEMA/HOHEMA) copolymer. Opacification was progressive, whitish, and generalized, and developed 4 to 15 months after surgery. The appearance resembled a mature cataract. All 3 patients showed a significant reduction in vision. There was no response to Nd:YAG laser treatment, and all 3 IOLs had to be explanted. The explanted lenses were analyzed with electron microscopy, elemental analysis, Fourier Transform (FT) Raman spectroscopy, and x-ray diffraction to define the nature of the opaque material. Results showed electron-dense deposits in the superficial 5 µm of the lenses. The deposits were predominantly composed of calcium and phosphorus, and x-ray diffraction identified the presence of hydroxyapatite. The polymer structure of the lens was unaltered.

Report of Cases. Case 1. A 67-year-old man underwent phacoemulsification on his left eye and IOL implantation in July 1998. He had diabetes, was taking insulin, and had had macular grid laser treatment for diabetic macular edema. Her best-corrected visual acuity went from 20/400 before surgery to 20/100 three months afterward. Opacification of the IOL developed 9 months after surgery, and best-corrected visual acuity dropped to 20/200. An IOL exchange was done in August 1999.

Case 2. A 72-year-old woman underwent phacoemulsification on her right eye and IOL implantation in June 1998. She had diabetes, was taking insulin, and had had macular grid laser treatment for diabetic macular edema. Her best-corrected visual acuity went from 20/400 before surgery to 20/100 three months afterward. Opacification of the IOL developed 15 months after surgery, and his visual acuity became perception of hand motions at 17 months. An IOL exchange was done in December 1999.

Case 3. A 79-year-old man underwent phacoemulsification on his right eye and IOL implantation in June 1998. He was in good overall health. His best-corrected visual acuity improved from 20/200 before surgery to 20/50 three months afterward. Intraocular lens opacification developed 9 months after surgery, and his visual acuity became perception of hand motions 15 months after surgery. An IOL exchange was done in August 1999.

All 3 patients were given local anesthesia and underwent clear corneal phacoemulsification. Sodium hyaluronate/chondroitin sulfate sodium (Viscoat; Alcon Surgical, Fort Worth, Tex) and balanced salt solution (BSS Plus; Alcon Surgical) with added adrenaline (0.1 mL of 1:1000 adrenaline in 500 mL BSS Plus) were used intraoperatively. Acetylcholine chloride (Ciba Vision Ophthalmics, Atlanta, Ga) was used for patients 2 and 3. No surgical complications were noted. For 1 month following surgery, all patients received 1% dexamethasone sodium phosphate and 1% neomycin sulfate eyedrops. We used the same intraoperative agents to implant about 500 IOLs from 1997 to 1999. Most patients were not affected by IOL opacification.

Methods. Each explanted lens was submitted to the pathology laboratory in a dry, sterile container without fixatives. All 3 lenses underwent the same tests. They were examined under both a dissecting microscope and a light microscope. Each lens was then cut into several pieces with a razor blade and subjected to transmission electron microscopy (TEM), scanning electron microscopy (SEM), elemental analysis, FT Raman spectroscopy, and x-ray diffraction. Several unused IOLs served as controls.

For TEM analysis, the lens was cut into 1-mm³ blocks and fixed in a solution of 1.5% cacodylate-buffered glutaraldehyde, postfixed in a solution of osmium tetroxide, dehydrated in a series of ethanol, and embedded in a resin block (Polybed 812; Polysciences Inc, Warrington, Pa). Ultrathin sections were stained with uranyl acetate–lead citrate and examined with TEM (Philips CM100; Philips Electron Optics, Eindhoven, the Netherlands) at an accelerating voltage of 80 kV.

For SEM analysis, 1-mm³ blocks of lens material were sampled and fixed in a solution of glutaraldehyde, postfixed in a solution of osmium tetroxide, dehydrated in a series of ethanol, and dried with carbon dioxide in a critical point dryer (Bal-Tec CPD 030; Bal-Tec AG, Liechtenstein). They were mounted on aluminum stubs and coated with gold and palladium in a sputter coater (Bal-Tec SCD 005; Bal-Tec AG). The specimens were examin-
ined with SEM (Leica Stereoscan 360; Leica Instruments Ltd, Cambridge, England).

For elemental analysis, 1-mm³ blocks of lens were air-dried and analyzed with an energy-dispersive spectrometer (Link eXL system; Link Analytical Ltd, Bucks, England) attached to the Leica Stereoscan 360.

For FT Raman spectroscopy, the sample was studied with an FT Raman spectrometer (FT-Raman; Bio Rad, Hercules, Calif), and the Nd:YAG laser (1064 nm) was used as the excitation laser source.

For powder x-ray diffraction, the test was performed with an x-ray diffractometer (Siemens D5000; Siemens, Munich, Germany) using CuKα radiation (wavelength = 1.5406 Å), and copper was used as the generating source.

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Results. Test results were similar for all 3 lenses. The lenses were semi-opaque on gross examination. Under the dissecting and light microscopes, both the anterior and posterior surfaces were reticulated, similar to a piece of dried leather.

With TEM analysis, the explanted lenses showed an undulating surface. The distance between the top of the elevated area and the bottom of the depressed area was approximately 10 µm. Electron-dense aggregates, which extended to a depth of 5 µm, were present along the superficial part of the lenses. The size of these aggregates varied, with the largest measuring approximately 1 µm. They were larger and more numerous near the surface (Figure 2). The aggregates contained needle-shaped crystalline deposits, which contrasted with the smooth surface and absence of deposits in the control IOL.

SEM analysis revealed that the explanted lens surfaces were irregular and had a “cerebriform” appearance, with convolutes of elevated areas alternating with crevices. This 3-dimensional architecture corresponded to the 2-dimensional appearance with TEM analysis (Figure 3). The control IOL revealed a smooth surface.

Elemental analysis showed calcium, phosphorus, oxygen, carbon, and trace amounts of sodium and magnesium present on the explanted lenses (Figure 4). Only carbon and oxygen were found on the control IOL.

The explanted lenses and the control IOL showed essentially the same features with FT Raman spectroscopy, indicating that they were the same type of polymer.

With x-ray diffraction, the explanted lenses showed a diffused halo at approximately 2θ = 16°-24° (where 2θ describes the range of angle between the incident x-ray and the test sample), which was due to the amorphous polymer matrix. The peaks at 2θ = 25.9°, 31.9°, 32.1°, and 33.1° (Figure 5) matched the major diffraction peaks for a typical hydroxyapatite sample. These peaks were absent on the control IOL.

Comment. Intraocular lens calcification has not been frequently reported. Olson et al² reported intraoperative calcification of the IOL surface. Bucher et al³ reported the formation of calcium hydroxyapatite on a polyHEMA IOL on the first postoperative day. The clinical features they reported were very different from the delayed calcification observed in our patients.

Bucher et al³ attributed IOL calcification to the use of phosphate-
containing solutions during surgery. We used balanced salt solution and viscoelastics, both of which contained calcium and/or phosphate. Following surgery, patients were given eyedrops that contained the steroid dexamethasone sodium phosphate. Materials used during surgery may explain early postoperative calcification, but this does not necessarily explain calcification several months afterward.

Normal aqueous humor contains calcium and phosphate. This continuous supply of minerals is a more convincing explanation for the delayed and progressive calcification in our patients. In addition, hydrogels are permeable to aqueous humor. The small amount of sodium and magnesium detected probably came from the aqueous carried by the explanted lenses. Carbon and oxygen were detected in both the explanted lenses and the control. Oxygen probably existed together with phosphorus in the form of hydroxyapatite. The presence of carbon may not be abnormal; more investigation is necessary to clarify its presence in the deposit.

The bulk of deposits were found just beneath the IOL surfaces. The physical presence of the deposits led to expansion of the superficial layers and subsequent surface folding, which produced the cerebriform appearance. Hydrogels make up a large family of polymers, and certain hydrogels are very active in promoting calcification. Winter and Simpson reported the calcification of synthetic polyHEMA sponges implanted into young pigs. The calcified IOL reported by Bucher et al was also made from polyHEMA. We believe that the calcium affinity of the HEMA/HOHEMA copolymer is comparable with that of polyHEMA and is an important factor leading to IOL calcification.

Most of the IOLs we used remained transparent after implantation. Although we believe that the calcium affinity of the polymer is responsible for calcification, this cannot explain its occurrence in only a handful of patients. Multiple factors might be involved, such as irregularities in IOL manufacturing, interaction with intraoperative materials, and patient factors such as race and diabetes mellitus. More investigation is necessary to determine the mechanism of calcification and the factors involved.

In conclusion, we observed delayed opacification of 3 IOLs that necessitated explantation 12 to 18 months after implantation. The opacification was caused by compounds containing calcium and phosphorus, specifically hydroxyapatite. Irregularly shaped deposits formed beneath the surfaces of the lenses, giving the surfaces a cerebriform irregularity. The calcium and phosphorus in the deposits were probably derived from the patients’ aqueous humor. We believe that the affinity of the hydrogel copolymer to calcium was responsible for the dystrophic calcification in these 3 cases. Why this kind of opacification occurs in only a handful of patients remains unexplained, and further work is necessary to define the multiple factors that may be involved.

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**Latanoprost and Periocular Skin Color Changes**

A 17 phenyl–substituted prostaglandin analog, 0.0005% latanoprost decreases intraocular pressure by increasing uveoscleral outflow. Since its introduction in 1996, several adverse effects have been reported, prominent among which has been increased pigmentation of the iris and eyelashes. Although darkening of the periocular skin is listed as an adverse effect in the product insert, it has never been reported in the literature to our knowledge. We describe 1 patient who had increased pigmentation of the periocular skin with the use of latanoprost eye drops and decreased pigmentation within 2 months of discontinuation of treatment with the eye drops.

**Report of a Case.** A 75-year-old woman with a 2-year history of open-angle glaucoma began using 0.005% latanoprost eye drops in June 1998. In September 1999 she reported that the skin around her eyes was much darker than the rest of her face (*Figure 1*). She stated that this darkening had occurred gradually during the past year. She was told to discontinue use of the eye drops in both eyes. When she was seen 1 month later, a discernible lightening of the periocular skin was noted. Two months after discontinuing the use of latanoprost eye drops, the periocular skin color was significantly lighter (*Figure 2*) and was unchanged 1 year later.

**Comment.** The first reported and most prominent adverse effect of latanoprost eye drops is darkening of the irides, with an initial reported incidence of 1% to 8%.1-3 A more recently reported adverse effect is hyperpigmentation of eyelashes as well as an increase in length and number.4,5 Both of these adverse effects are related to the melanogenic effect of prostaglandins. The best-known stimulant of melanogenesis is UV light. How UV light causes darkening of the skin is still uncertain, but it does cause the epidermal release of various eicosanoids, including prostaglandins.6 Prostaglandin is one of the most potent stimulants of melanogenesis7 and melanocyte growth.8

Our patient developed hyperpigmentation of both eyelids while using only latanoprost, and the condition resolved gradually during the 2 months after discontinuation use of the medication. We have seen 2 other cases of increased periocular pigmentation, 1 bilateral occurrence after 3 years of exposure to latanoprost and 1 ipsilateral occurrence after 18 months of exposure to latanoprost. Unfortunately, photographs to accurately document these cases for publication were not of good enough quality.

Pharmacia & Upjohn (Peapack, NJ) maintains a worldwide adverse experience system (WAES), a voluntary self-report database for adverse effects of Pharmacia & Upjohn products. Through September 1999, there have been fewer than 40 reports of pigmentedary changes to the skin in patients using Xalatan (latanoprost) eye drops (written com-
Most have involved darkening of the skin of the eyelids and periorcular region. There were a few reports of hyperpigmentation of the neck, back, or temporal area of the face. One report of vitiligo and another of periorcular depigmentation in a black woman were received by the WAES. The reported time of occurrence ranged from 3 weeks to 1 year after initiation of Xalatan therapy, and the patients involved were mostly women aged 47 to 80 years. Since the end of 1999, there have been 13 reports recorded at the National Registry of Drug-Induced Ocular Side Effects (NRDIOSE) of periorcular skin color changes purportedly caused by latanoprost (written communication, Frederick T. Fraunfelder, MD, February 10, 2000). The WAES and NRDIOSE case reports are unsolicited and nonsubstantiated and may not always represent valid adverse effects of a medication. Interestingly, a search of various medical databases from 1964 through January 2000 showed no report of hyperpigmentation of periorcular skin associated with the use of latanoprost eye drops. There has been only 1 report of hyperpigmentation of periorcular skin from a topical eye drop; this involved a patient using a β-blocker. 6

As with the initial report of hyperpigmentation of the eyelashes, we suspect that increased awareness of periorcular skin changes as an adverse effect of latanoprost will reveal a more widespread prevalence than previously suspected. It should be recognized, however, that the changes in pigment of the iris, eyelashes, and periorcular skin seem to be benign and of little more than cosmetic consequences. Furthermore, the skin changes seem to be reversible with discontinuing use of the medication. The transit time from the basal layer to the stratified corneum is 4 to 5 weeks, and shedding of the cornified layer requires 2 weeks more. Thus, it takes at least 7 weeks for skin pigmentation to disappear after discontinuing use of the medication, consistent with one of our patients. In contrast, iris melanocytes remain stable and changes in iris pigmentation after latanoprost use persist or regress very slowly. Patients should be warned that periorcular skin color changes could occur but that this adverse effect is reversible and should not detract from the benefits of this effective medication.

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Iris Atrophy, Cataracts, and Hypotony Following Peripheral Ablation for Threshold Retinopathy of Prematurity

The Cryo-ROP study established exo-cryotherapy as a beneficial treatment for threshold retinopathy of prematurity (ROP). 1 More recently, the diode and argon indirect lasers have been used to treat threshold ROP because they are technically easier to use and more easily tolerated by the patient compared with cryotherapy. 2-5 In addition, it has been demonstrated that a more confluent laser pattern has a higher success rate than a less confluent laser pattern. 6 Previously reported complications of cryotherapy include conjunctival and subconjunctival hemorrhage, conjunctival laceration, elevated intraocular pressure (IOP), and vision-threatening preretinal, retinal, or vitreous hemorrhage. 7,8 Reported complications of laser therapy include cataract development and hypophemas, and very rarely corneal, iris, and lens burns and choroidal rupture with hemorrhages and subsequent neovascularization. 9-11

We report on cataracts, iris atrophy, and hypotony in 8 eyes of 5 patients following confluent treatment for threshold ROP. None of the eyes demonstrated a retinal detachment at the time the anterior segment changes were identified. We feel that this represents an anterior segment ischemia.

Patients and Methods. Five patients were referred to William Beaumont Hospital in Royal Oak, Mich, from January 1997 to July 1999 for evaluation of complications from treatment of threshold ROP at various medical centers in the United States. All 10 eyes of the 5 patients had been treated for threshold ROP. Seven of the eyes that developed additional complications had been treated with diode laser and 1 eye had been treated with cryotherapy. All 7 eyes underwent lensectomy and vitrectomy. Two of the 7 eyes received silicone oil.
had a normal IOP and anterior seg-
view of the posterior pole. The left eye
large lens pearls, which reduced the
with evidence of iris atrophy and had
evaluation. The right eye was soft
lateral hyphemas and cataracts. Par-
ment for both eyes and developed bi-
patient received confluent laser treat-
6 days. At 8 weeks of age (33 weeks'
hyphema and hypotony. A lensec-
tomy, vitrectomy, sector inferior iri-
esthesia revealed regressed ROP in
both eyes and had the cysts and lens
surgically removed from the right eye.
The retina was attached and demon-
scribed attachment to the retina and sug-
gested regression of ROP. The patient
underwent a vitrectomy, membrane
peeling, and removal of retained lens
materials in both eyes. Subsequent
follow-up examinations showed both
eyes to be phthisical.

Case 3. A 705-g baby was born after
24 weeks 3 days' gestation. The patient
developed threshold ROP in both eyes at
8 weeks of age (33 weeks' PCA) and was treated with
confluent laser treatment to both
eyes. The left eye responded to the
laser therapy and the retinopathy regres-
sed. The right eye subse-
quently developed large pupillary
cysts and a cataract and became hy-
potonous.

The patient was referred to
William Beaumont Hospital for
evaluation and had the cysts and lens
surgically removed from the right eye.
The retina was attached and demon-
strated evidence of regressed ROP;
however, the eye went on to de-
velop phthisis.

Case 4. A 790-g baby was born at
25 weeks' gestation. The patient
went on to develop threshold ROP in
both eyes and was treated with laser
photocoagulation in both eyes at 38
weeks' PCA. Following laser treat-
ment, the baby developed severe post-
treatment anterior segment inflam-
ination in both eyes and bilateral
cataracts. One month after laser treat-
ment, the patient underwent bilat-
eral lensectomies and vitrectomies.
Two months after surgery the child
was referred to William Beaumont
Hospital and the right eye was found,
despite regressed ROP, to have de-
veloped early phthisis. The left eye
went on to develop a retinal detach-
ment secondary to advancing ROP
and was treated with a second vitrec-
tomy and membrane peeling. This eye
also went on to develop phthisis.

Case 5. A 632-g baby was born at
24 weeks' gestation. The patient de-
veloped threshold ROP in both eyes
and at 14 weeks of age (38 weeks' PCA)
was treated with confluent las-
er treatment to both eyes. After treat-
ment, both eyes developed cata-
acts, iris atrophy, and hypotony
(Figure).

The patient was referred for eval-
uation and underwent lensec-
tomy, vitrectomy, sector inferior iri-
dotomy, and placement of silicone
oil in both eyes. A follow-up exam-
ination with the patient under anes-
thesia 1 week later revealed the IOP
to be 10 to 12 mm Hg. Fundus ex-
amination of both eyes demon-
strated complete laser treatment,
retinal attachment, and regressed
ROP. Postoperative examination, 6
months after placement of silicone
oil, revealed a well-formed anterior
chamber, and ocular pressure, and
globe contour were both normal.

Results. Eight eyes were evaluated
for complications following treat-
ment for threshold ROP and found
to have signs of anterior segment is-
chemia including cataracts, iris at-
rophy, hypotony, and corneal haze.
Four of the 5 patients were male
and 5 of the eyes were right eyes. The
birth weights ranged from 570 to 790
with a mean of 657 g. The PCA
at the time of initial treatment for
threshold ROP ranged from 33 to 38
weeks with a mean of 35 weeks.

Six of the 8 eyes underwent len-
sectomy and vitrectomy with a fluid-
air exchange and yet still went on to
develop phthisis. Two of the 8 eyes
underwent lensectomy and vitrec-
tomy and received silicone oil in-
stead of a fluid-air exchange. These
eyes had a beneficial anatomical
result from this therapy.

Comment. Treatment for ROP,
whether with cryotherapy or laser,
has clearly proven to be beneficial
but is not without complication. This
article sites vision and ocular threat-
ening complications from confluo-
ent laser or cryotherapy of threshold
ROP. Clinical examination of all
eyes during examination with the
patient under anesthesia or at the
time of lensectomy or vitrectomy re-
vealed confluent anterior retinal
treatment, regression of threshold
ROP, and the absence of a retinal de-
tachment in all the eyes. In addi-
tion, it should be noted that the cili-
ary body was not accidentally treated
in any of the cases reported.

A possible mechanism for de-
veloping anterior segment ische-
emia following treatment of ROP can
be made by comparing laser treat-
ment in proliferative diabetic reti-
nopathy with laser treatment in ROP.
The major difference in treating
these diseases is the location and confluence of the laser burns. Laser burn placement for the treatment of proliferative diabetic retinopathy tends to spare the far peripheral portions of the retina. Treatment of ROP includes the entire anterior avascular retina from the edge of the pars plana back to the anterior edge of the ridge of proliferative retinopathy covering the entire circumference of the far peripheral retina. The long posterior ciliary arteries travel along the horizontal meridians in the suprachoroidal space and anastomose with the anterior ciliary arteries to form the anterior vascular arcade and supply the anterior segment of the eye with blood. In addition, during treatment of ROP there is significant scleral depression, which could impair the circulation in the long posterior ciliary arteries. Furthermore, treatment in the horizontal meridians tends to be more confluent than in other areas because these sectors of retina are more accessible with relation to the medial and lateral canthi. Impairment of blood flow and simultaneous confluent tissue ablation could increase the risk of inducing anterior segment ischemia that includes cataract, iris atrophy, and hypotony.

A potential treatment to preserve the physical structure of the eye after this reported complication is with the use of silicone oil. The 2 eyes in which silicone oil was placed maintained normal anatomic structure compared with the eyes that only had a fluid-air exchange and went on to become hypotonous. The adult and pediatric literature has reported on the safety of silicone oil used for extended periods.\(^1\)\(^2\)\(^3\) It should be noted that follow-up for the eyes with silicone oil was for 6 months; therefore, it is possible that the anatomic success is only temporary. There are reported side effects of using silicone oil, but at this time we feel this treatment provides the best possible outcome for a difficult complication of ROP treatment.

It has been the impression of many clinicians that confluent is a more effective treatment than non-confluent laser. We have identified a complication of confluent treatment, but it may be avoided. Perhaps one should treat with more space between laser burns or cryo-spots for the clock hours position of the retina in the horizontal meridians to decrease the risk of ablating the long ciliary arteries. This report should not discourage physicians from being aggressive with the treatment of ROP but instead should prompt investigation to further advance our methods of treatment and our understanding of its complications.

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Primary Intraocular Lymphoma Seen With Transient White Fundus Lesions Simulating the Multiple Evanescent White Dot Syndrome

We describe 3 patients with multifocal, white, deep retinal lesions simulating the multiple evanescent white dot syndrome (MEWDS). The retinal lesions waxed and waned in each patient. All patients were eventually proven to have primary intraocular lymphoma. Our 3 cases expand the spectrum of unusual, recognized clinical features of primary intraocular lymphoma.

Report of Cases. Case 1. A 58-year-old man had a 1-month history of decreased visual acuity in the right eye. Ocular history included a diagnosis of possible MEWDS in the left eye. Small white dots in the retina resembling MEWDS (Figure 1A) were noted. These grew into tumor-like masses. Two years later the left eye was blind and painful; enucleation was performed and revealed intraocular large cell lymphoma with optic nerve involvement. The patient received radiation treatment to the brain and orbits. The patient first visited us with a 1-month history of worsening vision in the right eye, which had a visual acuity of 20/40. Fundus examination revealed scattered gray-white granular lesions of the deep retina clustered in the mid-peripheral fundus (Figure 1B). These lesions resembled the lesions noted previously in the left eye. Magnetic resonance imaging of the head and orbits revealed lymphoma. On follow-up, the patient’s visual acuity decreased to counting fingers. There was an increase in the number and size of white lesions present in the right fundus, which was consistent with intraocular lymphoma. The patient underwent radiation treatment in the right eye, with improvement of visual acuity to 20/30. On his most recent follow-up, 9 years after the initial visit, the patient was...
noted to be free of ocular or cerebral lymphoma; however, the visual acuity of the right eye was no light perception, secondary to radiation optic neuropathy and retinopathy.

Case 2. A 53-year-old woman had experienced worsening vision in her right eye for 1 month. Visual acuity was 20/30 OD and 20/20 OS. Examination of the right fundus revealed multiple whitish outer retinal or subretinal lesions located above the superotemporal arcade (Figure 2A). A fluorescein angiogram of the right fundus showed stippled foci of late-appearing hyperfluorescence, with a subset of lesions in a wreathlike shape corresponding to the whitish fundus spots (Figure 2B). The clinical diagnosis was MEWDS. During the next month, the fundus lesions disappeared spontaneously, and the patient’s visual acuity returned to 20/20.

One year later the patient returned with spots in her right eye. Her visual acuity was 20/20 OD and 20/15 OS. The right fundus showed numerous flat, white, outer retinal or subretinal lesions measuring 250 µm to 500 µm in diameter along the superotemporal arcade, and similar lesions associated with turbid subretinal fluid along the inferotemporal arcade (Figure 3A). Multifocal chorioretinitis was suspected, but an extensive workup was negative for this.

During the next month, the patient’s visual acuity decreased to counting fingers OD. Examination showed an increase in the posterior subretinal fluid in the right eye, but the disappearance of the white fundus lesions along the superotemporal arcade (Figure 3B). Diagnostic vitreous biopsy results revealed neoplastic lymphoid cells consistent with the diagnosis of intraocular large cell lymphoma. The right eye was treated with radiation. After treatment, extensive macular subretinal fibrosis developed, and visual acuity decreased to hand motions OD.

Two years after ocular diagnosis and treatment, despite whole-brain radiation, the patient died of central nervous system lymphoma.

Case 3. A 53-year-old man had experienced worsening vision in his right eye for 2 weeks. Visual acuity was 20/40 OU. Fundus examination of the right eye revealed numerous small, white, deep retinal or subretinal lesions above the fovea that were consistent with MEWDS (Figure 4A). The patient was treated by his ophthalmologist with prednisone. During the next month, the white fundus lesions disappeared.
Three months later, the patient developed a localized area of superficial retinal infiltration with intraretinal hemorrhage in the inferotemporal region of the right eye. Infectious retinitis was suspected. The cause of the presumed retinitis was unknown. Despite his immune status being normal, he was empirically treated with intravenous ganciclovir. The retinal infiltrates resolved after 3 to 4 weeks, and the visual acuity increased to 20/25 OD. Four years after the original episode, the patient noted worsening vision in his left eye. Visual acuity was correctable to 20/25 OD, but only to counting fingers OS. Fundus examination of the left eye revealed multifocal yellow-white chorioretinal lesions in the posterior pole and superonasal region (Figure 4B). A fine-needle aspiration biopsy was performed, the results of which were consistent with the diagnosis of primary intraocular large cell lymphoma. The visual acuity in the left eye returned to counting fingers. To date, the patient is undergoing a course of external beam radiation therapy to that eye.

Comment. Primary intraocular large-cell (non-Hodgkin) lymphoma is an uncommon neoplastic disorder characterized by infiltration of the vitreous and retina by neoplastic lymphoid cells. Accumulation of large-cell lymphoma cells in geographic white to yellow-white lesions beneath the retinal pigment epithelium is the usual appearance. A variety of other presentations such as retinal infiltrates that can resemble viral retinitis; vascular sheathing; retinal vascular occlusions; and multifocal, tiny, deep retinal or superficial choroidal white lesions have been reported. The neoplastic lymphoid cells are almost always B cells. The disorder is frequently bilateral and can cause profound visual loss. Patients with primary intraocular lymphoma tend to be middle aged to elderly adults, and women seem to be affected more often than men. This disorder is usually associated with central nervous system lymphoma, which is often the cause of death in affected persons.

Primary intraocular lymphoma can be difficult to diagnose, especially in patients with unusual characteristics. Our 3 patients initially visited with unilateral, multifocal, small, whitish spots at the level of the outer retina. Initially each patient was believed to have MEWDS or a variant thereof. The partial or complete resolution of the lesions in these patients prior to developing more typical manifestations of lymphoma suggested MEWDS.
ever, all patients were in their 50s, and 2 of the 3 were men. Although MEWDS is occasionally seen in patients in this age group, it is very unusual. The diagnosis of MEWDS is suspect unless the lesions are absolutely classic. The absence of the classic foveal changes of MEWDS in all cases should also have suggested another diagnosis.

The possibility of primary intraocular lymphoma during the MEWDS-like phase of the disorder in all of the patients was not initially entertained. We now believe that the multifocal, whitish fundus lesions noted at initial visit were deep retinal or subretinal lymphomatous infiltrates. The fluorescein angiographic appearance in one of the patients was similar but not identical to the angiographic changes seen in patients with MEWDS. The mechanism that can induce clinical regression of the whitish fundus spots and a prolonged quiescent interlude before more typical lesions develop is unknown.

Primary intraocular large cell lymphoma should be included in the differential diagnosis of MEWDS, especially in patients older than 50 years. Clinicians must be aware that subtle, multifocal, deep retinal or subretinal lesions that wax and wane can rarely be manifestations of primary intraocular lymphoma. Diagnostic vitrectomy, along with magnetic resonance imaging and lumbar puncture, may be useful diagnostic modalities to rule out primary intraocular lymphoma in these patients.

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