Branch Retinal Artery Oclusion Caused by an Embolus of Metastatic Gastric Adenocarcinoma

We report a case of branch retinal artery occlusion caused by an embolus of metastatic gastric adenocarcinoma. A 67-year-old man sought treatment for sudden visual loss in his left eye. He had a medical history of gastric cancer with liver metastasis. Findings on funduscopic examination included localized edema of the inner retina consistent with a supratemporal branch retinal artery occlusion and a yellowish-white subretinal mass surrounding by shallow retinal detachment superior to the equator. Histopathological and immunohistochemical examinations of the eye obtained post mortem showed positive staining of the choroidal tumor for epithelial membrane and carcinoembryonic antigens. In addition, an embolus of tumor cells was found to cause occlusion of the retinal artery.

Occlusion of the retinal artery is mostly ascribed to either embolus, thrombus, or vasculitis. It is strongly associated with carotid atheromatous plaque or cardiac valvular diseases with vegetation. Other causes, such as atrial myxoma, temporal arteritis, periarteritis nodosa, and systemic lupus erythematosus, have been described but are relatively rare. Embolism caused by neoplastic cells is extremely rare. We report a case of gastric adenocarcinoma that metastasized to the choroid and occluded a branch retinal artery with an embolus of carcinoma.

Report of a Case. A 67-year-old man was referred to our clinic for sudden visual loss in his left eye. He had been diagnosed with gastric adenocarcinoma and metastatic liver cancer 2 years previously and had undergone total gastrectomy and partial resection of the liver. He had no history of hypertension, diabetes mellitus, heart disease, or cerebral infarction. On examination, the corrected visual acuity was 20/30 OD and light perception OS. Intraocular pressures were 13 mm Hg OD and 10 mm Hg OS. A relative afferent pupilary defect was observed in the left eye. External and slitlamp examinations were unremarkable bilaterally. Funduscopic examination revealed milky-white retinal edema consistent with branch retinal artery occlusion in the supratemporal quadrant and a yellowish-white subretinal mass surrounded by shallow retinal detachment in the superior quadrant of the left eye (Figure 1).

Ultrasoundography disclosed a mass with strong internal echoes in the same region, suggestive of a subretinal tumor. The provisional diagnosis of the mass lesion was metastatic adenocarcinoma to the choroid associated with branch retinal artery occlusion. Fluorescein angiographic and computed tomographic examinations could not be performed because of the patient’s poor general condition. Laboratory values included a carcinoembryonic antigen level of 722 ng/mL (reference level, <5 ng/mL) and a carbohydrate antigen level of 722 ng/mL (reference level, <37 U/mL). Cultures of arterial blood were negative for bacteria, and splenomegaly was absent. A chest radiograph showed no concrete evidence of a metastatic tumor. Three weeks after admission, the patient died because of the deterioration of his general condition. Both eyes were obtained post mortem, fixed in formaldehyde, and processed routinely for light microscopy. Macroscopic examination disclosed a solid tumor with a mottled dark-brown color that measured 12 mm × 6 mm in the choroid of the left eye. Microscopic examination of the tumor disclosed extensive infiltration of the choriocapillaris by cords and lobules of a malignant epithelial neoplasm consistent with metastatic mucin-secreting adenocarcinoma. The tumor cells formed tubules and glandular structures (Figure 2A), and the periodic acid–Schiff and alcian blue stains confirmed the presence of numerous intracytoplasmic vacuoles of mucin (Figure 2B). Immunohistochemical stains showed intense positive immunoreactivity for epithelial membrane antigen (Figure 3A) and carcinoembryonic antigen (Figure 3B). The histopathological findings of the choroidal metastasis resembled the patient’s primary tumor (Figure 4) and were consistent with a moderately well-differentiated gastric adenocarcinoma. A micrometastasis was also identified in the ciliary body inferior to the muscle. In addition, an embolus of tumor cells was found to totally occlude the lumen of the supratemporal retinal arteriole near the optic disc (Figure 5). The cytological characteristics of the tumor embolus were quite similar to those of the choroidal tumor. The right eye was normal on gross examination, and
there were no particular histopathological changes.

Comment. The present study clearly shows that the choroidal tumor was metastatic adenocarcinoma. Histopathological examination also confirmed that the supratemporal retinal arteriole was occluded by an embolus of tumor cells. The histopathological and immunohistochemical studies, including positive immunoreactivity markers for epithelial membrane antigen and carcinoembryonic antigen, are con-
sistent with metastatic gastric adenocarcinoma; a primary tumor with known hepatic metastasis had been treated 2 years earlier. The patient is presumed to have died from widespread systemic metastases because postmortem examination was limited to the eyes.

To our knowledge, retinal artery occlusion caused by an embolism of tumor cells is very rare, and there are only a few reports that clearly describe this condition. Occlusion of the central retinal artery by chondrosarcoma and bronchial carcinomas was described by Burde and Henkind and Tarkkanen et al., respectively. Zamora et al. reported a case of branch retinal artery occlusion in a patient with papillary fibroelastoma of the mitral valve, but there was no histopathological demonstration of the embolus. Metastasis of carcinoma cells to the retina alone appears to be a rare event. Smoleroфф and Agatston reported a case of gastrointestinal carcinoma that metastasized into the nerve fiber layer of the retina. Shields et al. studied 520 eyes with uveal metastasis and found only 5 to have metastatic lesions in the retina.

However, there was no description of arterial occlusion in their series. In patients with end-stage disease, particularly those with malignancies, embolism due to bacterial endocarditis, nonbacterial thrombotic endocarditis, or thrombi formed with disseminated intravascular coagulation syndrome may be encountered in the retinal artery. In the present case, there was no strong clinical or laboratory evidence of infection, valvular diseases, or disseminated intravascular coagulation. Complete obstruction of the arterial lumen by the tumor embolus as shown in our case is uncommon, whereas venous and lymphatic invasion by malignant cells is more common because it can be observed in routine surgical specimens. A major factor that contributes to the formation of tumor emboli is the expression of adhesion molecules, but embolicogenic factors such as those mentioned above may accelerate their formation.

In conclusion, we report a clinicopathological correlation of a case of metastatic gastric adenocarcinoma to the choroid that had branch retinal artery occlusion due to a tumor embolus. Ophthalmologists should be aware of this cause of acute visual loss in their differential diagnoses of retinal artery occlusion in patients with a history of malignancy.

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Report of a Case. A 63-year-old woman had bilateral cataract extractions with silicone IOL implants (model SI30NB; Allergan Inc, Irvine, Calif) in early 1995. Shortly after a normal eye examination, she began a 10½-month course of 300 mg of rifabutin, by mouth, once daily for chronic pulmonary MAC. At annual follow-up, both IOLs were noted to be discolored, and rifabutin therapy was discontinued.

Slitlamp examination revealed a distinct rose-color in both IOLs (Figure 1). The remainder of the ex-

Discoloration of Intraocular Lens Subsequent to Rifabutin Use

A 63-year-old woman developed discoloration of the silicone intraocular lens (IOL) implants in both eyes after receiving 300 mg of rifabutin by mouth, once daily, for 10½ months. Examination revealed a rose color to both implants, though the patient reported minimal visual deficit. We then investigated the effect of rifabutin on 3 different common IOL materials and found that it only affected silicone. Though rifabutin is well known to cause discoloration of body fluids and soft contact lenses, this case illustrates this process occurring in IOL implants.

Rifabutin is indicated for prophylaxis against Mycobacterium avium complex (MAC), which is primarily seen as a coinfection with human immunodeficiency virus (HIV). Shown to cause discoloration in certain body fluids, including tears, saliva, and perspiration, rifabutin prescribing guidelines specifically caution that soft contact lenses may be permanently stained subsequent to its use. However, to our knowledge, the occurrence in an IOL has not been documented. We describe a patient who developed a bilateral discoloration of her silicone IOLs.

amination was unremarkable, with visual acuity correctable to 20/20 OU. That both IOLs were equally and simultaneously stained is likely to account for the lack of perceived color shift. No further change in IOL coloration has been noted since discovery. Thus, the IOLs were not removed.

Comment. Silicone IOL engineering has achieved a high degree of long-term optical clarity so that reports of decreased clarity have become rare (approximately 0.07%).

This case represents a potentially significant effect on the patient’s quality of life because the stained lenses are intraocular.

The rifamycins are recognized as “standard-of-care” drugs against both tuberculous and atypical mycobacterial infections. Use of these drugs is increasing because the incidence of MAC has dramatically increased among both HIV-infected and immunocompetent individuals during the last decade. High rates of increase are currently being reported in patients older than 50 years.

These findings have potential implications for our elderly population, as many of these individuals may have already received silicone IOLs by the time that they develop MAC or infection from implantation of orthopedic hardware. Physicians should be thus cautioned in their use of rifabutin in patients with silicone IOLs, and that acrylic or polymethyl methacrylate lenses may be better suited for patients in whom opportunistic infections are likely.

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Delayed Luxation of a Lens Nucleus After Vitrectomy

Accidental lens damage occurs less than 1% of the time during vitrectomy for diabetic retinopathy and may necessitate concurrent lenscrotomy. 3, 4 We report an unusual late complication of pars plana vitrectomy—delayed luxation of the lens nucleus.

Report of a Case. A 52-year-old man with a 20-year history of diabetes mellitus sought treatment at the Parkland Memorial Hospital Ophthalmology Clinic, Dallas, Tex, because of redness and photophobia in the left eye for 3 days. One year previously, he underwent vitrectomy in the left eye for proliferative diabetic retinopathy complicated by nonclearing vitreous hemorrhage and neovascular glaucoma. Four months prior to the current development, he underwent a second vitrectomy in the same eye for recurrent vitreous hemorrhage. The surgeon noted no intraoperative complications, including lens touch with the instruments. On the first day after the second vitrectomy, best-corrected visual acuity was 20/400 OS, and a new posterior subcapsular cataract was noted.

On examination of the left eye, best-corrected visual acuity was hand motion at 1 ft. Circumcorneal hyperemia and keratic precipitates were noted on slitlamp biomicroscopy. The anterior chamber was deep, with
was resting on the retina. Raphy revealed that the lens nucleus was 12 mm Hg. B-scan ultrasonography revealed that the lens nucleus and posterior lens capsule were not seen. Intraocular pressure at the time of the operation was 20 mm Hg. The lens nucleus was wrinkled with an opacified anterior capsule and zonules were intact, but a large rent was found in the inferior posterior capsule.

Comment. After lens-sparing vitrectomy, the lens tends to fall slightly posteriorly, making accidental lens touch more likely during repeat vitrectomy. Our patient likely had an iatrogenic defect in the posterior capsule prior to luxation. The acute and persistent posterior subcapsular cataract seen after the second vitrectomy in our patient was likely due to direct trauma to the posterior lens. We theorize that increased intracapsular volume secondary to lens hydration caused extension of the posterior capsule defect and allowed the lens nucleus to fall into the posterior segment of the eye.

Luxation of the lens nucleus is an unusual late complication of vitrectomy. Cataract surgeons should be aware of the possibility of occult posterior capsule damage when performing cataract extraction after vitrectomy.

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Refractive, Topographic, and Visual Effects of Flap Amputation Following Laser In Situ Keratomileusis

A review of complications associated with laser in situ keratomileu-

Figure 1. A slitlamp photograph of the left eye shows a wrinkled anterior lens capsule with an opacified white anterior lens cortex.

Figure 2. A B-scan ultrasonogram of the left eye shows a lens nucleus that is dislocated into the posterior segment.
followed infectious keratitis and flap melting that results in some degree of scarring and opacification of the underlying corneal bed. Consequently, it has been difficult to predict what the optical qualities of the uninflamed stromal bed might have been. We document herein the corneal findings in 2 patients who underwent early flap amputation for noninflammatory epithelial ingrowth following LASIK.

Report of Cases. Case 1. A 46-year-old woman with a history of recurrent corneal erosion and an examination finding consistent with map-dot-fingerprint dystrophy underwent bilateral LASIK for the correction of an error of −6.75 + 0.50 × 100 OD and −7.00 + 0.25 × 072 OS. An automated microkeratome (Automated Corneal Shaper [ACS]; Bausch & Lomb Surgical, Rochester, NY) was used to create the corneal flaps with nasally located hinges, followed by ablation with an excimer laser (VISX Star, VISX, Inc, Santa Clara, Calif). An epithelial defect was produced during surgery in the left eye. A bandage soft contact lens was placed, but a defect persisted at the first follow-up visit 1 day later. Approximately 3 weeks later, epithelial ingrowth along the interface of the corneal flap and the bed was identified at the hinge and extended toward the entrance pupil. The flap was elevated and the interface epithelium, removed. Approximately 2 weeks later, the epithelial ingrowth had recurred, so the flap was amputated.

The patient was treated with a bandage contact lens, and ciprofloxacin hydrochloride solution was applied every 3 hours. No corticosteroids were applied. During the next 5 days, the epithelial defect created by removal of the flap closed, the bandage contact lens was removed, and the patient was prescribed diclofenac sodium solution for occasional use up to 3 times daily and artificial tears for lubrication. Approximately 1 week after closure of the epithelial defect, the uncorrected visual acuity in the left eye was 20/100. Automated refraction identified an error of −5.50 + 3.50 × 159, but the corresponding visual acuity was not recorded. Topical corticosteroids were prescribed for application 3 times daily and discontinued after 1 month. During the next 6 months, the corneal haze in the left eye was not recorded as being any greater than 1+. However, at 9 months after flap amputation, the uncorrected vision was recorded as 20/100, correcting to 20/40 with a refraction of −1.50 + 0.25 × 171.

The patient was referred to the University of California, San Francisco Refractive Surgery Service for further consultation in May 2001, approximately 2 years after LASIK and flap amputation of the left eye. At that time, she complained of fluctuating vision in the left eye that at its best remained blurred. She also reported ghosting and glare. Examination disclosed an uncorrected visual acuity of 20/25 OD and 20/80 OS. The vision of the left eye improved to 20/25 with a refraction of −3.25 + 3.25 × 70.

Slitlamp biomicroscopic examination of the right eye showed a well-positioned, nasally hinged corneal flap, but coarse, diffuse epitheliopathy. There was no evidence of subepithelial or stromal haze or scarring, except for a normal degree of scar formation outlining the edges of the corneal flap. Slitlamp examination of the left eye showed a subtle, vertically oriented elevation of the corneal surface at the hinge of the amputated flap. There was no evidence of subepithelial or stromal scarring, either at the former location of the flap edge or over the central cornea. However, there was a moderate degree of epithelial irregularity evident without instillation of fluorescein sodium dye. Fluorescein sodium staining revealed coarse, diffuse epitheliopathy concentrated over the central cornea and an area of irregular surface contour that appeared to involve the central area of corneal dissection that produced the amputated flap.

Computerized corneal mapping (Figure 1) confirmed the relative irregularity of the left eye. A topographic map of the right eye (Tomey Topographic Modeling System, version 2.3.6; Tomey Corp, Waltham, Mass) showed a simulated keratometry reading of 40.01 × 41.07@91° with a surface regularity index of 0.52 and a surface asymmetry index of 0.18. However, a topographic map of the left eye produced a simulated keratometry reading of 40.90 × 42.51@103° with a surface regularity index of 0.50 and a surface asymmetry index of 1.25. On comparing the right and left eyes, a markedly asymmetrical reflex was also observed on retinoscopy with significantly greater irregularity noted in the left eye.

Although a relatively high degree of astigmatism was noted in the
left eye, the spherical equivalent was calculated to be \(-1.625\) diopters (D). Since the refraction in the right eye was \(-1.50 + 1.00 \times 090\), anisometropia was limited, so spectacles were prescribed to improve visual function.

**Case 2.** A 33-year-old man underwent bilateral LASIK for the correction of an error of \(-1.75 + 0.50 \times 30\) OD and \(-2.00 + 0.25 \times 160\) OS. An automated microkeratome (ACS; Bausch & Lomb Surgical) was used to create the corneal flaps. A large epithelial defect was created in the left eye, so the flap was repositioned without excimer laser ablation. A bandage contact lens was placed to promote epithelial healing. Approximately 2 months later, the patient returned to surgery. A corneal flap with a nasal hinge was created in the left cornea using an automated microkeratome (ACS; Bausch & Lomb Surgical), and the ablation was performed using an excimer laser. An epithelial defect was noted at the end of the procedure, and a bandage contact lens was kept in place for the next 3 days. One week after surgery, uncorrected vision was 20/40 OS, correcting to 20/25 with a refraction of \(-1.00 + 1.50 \times 20\). No significant epithelial ingrowth was noted.

Two weeks later, the patient returned with the complaint of ocular discomfort in the left eye. Uncorrected vision was 20/30−. Epithelial ingrowth was noted along the nasal hinge, with extension toward the entrance pupil. At that visit, the flap was lifted to remove the interface epithelium, and the epithelium overlying the flap was noted to be friable. On the basis of anticipated difficulties with recurrent epithelial ingrowth, the flap was amputated and a bandage contact lens was placed. Ciprofloxacin and diclofenac solutions were prescribed 4 times daily. The epithelial defect healed during the next few days, and 1 week after flap amputation the uncorrected visual acuity was 20/200, correcting to 20/60 with a refraction of \(-5.00 + 1.50 \times 100\). The ciprofloxacin solution was discontinued, and corticosteroid drops were prescribed for use 3 times daily. Two months later, the uncorrected vision was 20/100, correcting to 20/50− with a refraction of \(-4.75 + 2.00 \times 105\). The corticosteroid therapy was reduced to 1 drop per day and then discontinued.

The patient complained of poor vision and nighttime glare and halo and was referred to the University of California, San Francisco Refractive Surgery Service for consultation in May 2001, approximately 18 months after LASIK and subsequent flap amputation of the left eye. Examination at that time disclosed an uncorrected visual acuity of 20/25 OD, correcting to 20/20 with a refraction of \(-0.50 + 0.50 \times 55\), and an uncorrected visual acuity of 20/60 OS, correcting to 20/20− with a refraction of \(-3.75 + 3.75 \times 97\). Pachymetry readings were 532 µm OD and 439 µm OS.

Slitlamp biomicroscopic examination of the right eye showed a well-positioned, nasally hinged corneal flap with mild central subepithelial opacification, whereas slitlamp examination of the left eye was remarkable for mild vertical linear elevation at the site of the transected hinge, a semicircle of subepithelial haze reminiscent of surface photorefractive keratectomy (PRK)–associated scarring that appeared to outline the perimeter of the flap, and a relatively lucent central cornea overlying the entrance pupil. (Figure 2) The surface of the central cornea appeared to be relatively smooth, but upon instillation of fluorescein sodium solution, inspection of the tear film pattern indicated an irregular surface. The irregularity of the left eye’s corneal surface was confirmed by computerized corneal mapping (Figure 3). A topographic map of the right eye produced a simulated keratometry reading of 42.27 × 43.32@84°, with a surface regularity index of 0.11 and a surface asymmetry index of 0.50. However, a topographic map of the left eye showed a simulated keratometry reading of 43.57 × 46.40@115°, with a surface regularity index of 1.62 and a surface asymmetry index of 0.86. On comparing the right and left eyes, a markedly asymmetrical reflex was also observed on retinoscopy, with markedly greater asymmetry noted in the left eye.

Since the acuity in the left eye could be corrected to 20/20− with a relatively low degree of anisometropia based on spherical equivalent, spectacles were recommended, but the patient adamantly refused to consider spectacle correction. Rigid contact lenses were also suggested, but the patient elected to forgo fitting.

**Comment.** The findings from large reported series of complications seen in consecutive cases of patients who have undergone LASIK suggest that most complications can be attributed to abnormalities of the corneal flap that translate to irregularity or opacification of the anterior cornea. If amputation of the corneal flap were followed by reepithelialization...
and smoothing of the corneal surface (analogous to corneal healing after surface PRK) without the introduction of significant scarring, refractive error, or irregularity, then this approach might prove useful in addressing most postsurgical complications of LASIK. Unfortunately, few reports in the literature provide a guide to the clinical course that can be expected after flap amputation in the uninfected cornea. Patel and colleagues\(^4\) have demonstrated that significant corneal smoothing occurs from 3 months to 12 months after PRK, presumably as a result of stromal healing and remodeling. Using very high-frequency ultrasound scanning, Reinstein and colleagues\(^5\) examined corneas that had undergone LASIK and reported regional variations in epithelial thickness that tended to compensate for underlying stromal irregularity, thereby reducing corneal irregularity. In the 2 cases we present, it is discouraging that reduced best spectacle-corrected visual acuity with correspondingly elevated indices of asymmetry and irregularity was evident 18 months and 2 years after flap amputation. Therefore, it is questionable how much further improvement in surface regularity might occur during subsequent months or years.

In neither case was there substantial scarring of the corneal stroma overlying the entrance pupil that was subjected to excimer ablation. High degrees of refractive error corrected by surface PRK are expected to be associated with a greater risk of scarring, and it has been suggested that this scarring is related to the depth of the ablation performed.\(^6\) However, after flap amputation, relatively deep layers of the cornea were exposed to the epithelium after healing, and no significant haze was recorded throughout the healing period. This finding suggests that the risk for haze formation in PRK probably goes beyond simple considerations of exposure of the deeper stroma devoid of Bowman membrane to healing epithelium. Rather, these cases suggest that flap amputation is not necessarily followed by significant central corneal haze and scarring.

Nevertheless, the refractive and topographic outcomes of our 2 patients indicate that there is a substantial risk for refractive change and induction of irregular astigmatism following flap amputation. Any characteristic pattern of induced astigmatism is probably related to the path followed by the microkeratome in creating the flap, which in turn will be related to the particular design of the microkeratome. Since there were no other flap-related abnormalities beyond epithelial ingrowth in these cases, we surmise that flap amputation...
tion was performed because it was seen as a definitive treatment of the ingrowth that would produce acceptable surface smoothing over time.

The first patient we describe had a history of recurrent erosion syndrome, which presents an increased risk for epithelial ingrowth, keratolysis, flap melting, and loss of best corrected visual acuity. For this reason, LASIK is not recommended in the setting of anterior basement membrane disease, and PRK should be considered. Such severe complications might indeed ultimately necessitate flap amputation, but no such progression was seen in the cases reported herein. Therefore, based on the observed long-term clinical course, we suggest that in the absence of compelling indications (such as gross flap irregularities or interface infection in which the flap might limit antibiotics penetration), flap amputation should be a last resort in the management of flap complications.

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Intravitreal Triamcinolone Acetonide as Treatment for Macular Edema From Central Retinal Vein Occlusion

Central retinal vein occlusion (CRVO) is a common retinal vascular disorder that can lead to significant visual disability. Persistent macular edema is one of the major complications associated with CRVO. The Central Vein Occlusion Study evaluated the efficacy of intravitreal laser photoagulation in patients with macular edema caused by CRVO. This study did not find a difference in visual acuity between treated and untreated eyes at any stage during the follow-up period. Therefore, there is currently no proven management for macular edema in the setting of CRVO. The purpose of this interventional case report is to describe the clinical course of 2 patients with macular edema secondary to CRVO who underwent intravitreal injection of triamcinolone acetonide.

Report of Cases. Case 1. A 57-year-old man had a 2-month history of decreased visual acuity in his right eye. On initial examination, his best-corrected visual acuity was 20/40 OD and 20/20 OS. Results of anterior segment examination were remarkable only for 2+ nuclear sclerosis in both eyes. Intraocular pressure was 15 mm Hg OD and 19 mm Hg OS. A dilated fundus examination revealed a nonischemic CRVO with macular thickening or visual acuity loss of more than 600 µm on OCT.

The patient was observed for an additional month, and when there was no improvement in the degree of macular thickening or visual acuity, an intravitreous injection of 4 mg (40 mg in 1.0 mL) of triamcinolone acetonide was given in the right eye.

Follow-up 1 month later showed a return of visual acuity to 20/25 OD, with complete resolution of macular edema on both clinical examination (Figure 2A) and OCT (Figure 2B). Intraocular pressure was unchanged, and the improvement in visual acuity and clinical examination results remained at the 6-month follow-up.

Case 2. A 67-year-old man had a 1-month history of decreased visual acuity in the left eye. Examination revealed a normal fundus with CRVO and macular edema. Results of anterior segment examination were remarkable for 2+ nuclear sclerosis in both eyes. Intraocular pressure was 10 mm Hg OU. A dilated fundus examination revealed a normal fundus in the right eye. Examination of the left fundus revealed findings consistent with an ischemic CRVO. Foveal thickness was greater than 600 µm on OCT.

The patient was followed up at 2-month intervals for the next 8 months. Although the intraretinal hemorrhage cleared significantly, there was neither improvement in visual acuity nor a decrease in the amount of macular edema noted on clinical examination or OCT.

Because there was no clinical improvement, an intravitreous injection of 4 mg of triamcinolone acetonide (40 mg in 1.0 mL) was given.

Figure 3 shows the extent of macular edema noted on both slitlamp biomicroscopy and OCT 5 days before treatment. Three weeks following treatment, his visual acuity improved to 20/100 OS, and a fundus examination revealed a significant decrease in macular edema.

Foveal thickness measured with OCT was...
100 µm. At the 2-month follow-up, there continued to be a reduction in macular edema on clinical examination and OCT (Figure 4).

The patient did well until 3 months following the injection, when his visual acuity decreased to 20/400. Macular edema was noted on slitlamp biomicroscopy, and foveal thickness was 500 µm on OCT. No further intervention was attempted at this point, and the patient has been observed with no change in his clinical status.

Comment. Triamcinolone acetonide is a corticosteroid that is commercially available, inexpensive, and commonly used as a periocular injection for the treatment of cystoid macular edema occurring secondary to uveitis or resulting from in-
traocular surgery. Intravitreous triamcinolone acetonide has been used experimentally in the prevention or treatment of proliferative vitreoretinopathy, retinal neovascularization, choroidal neovascularization, and most recently for macular edema secondary to diabetic retinopathy. In these 2 patients, we attempted to reduce macular edema secondary to CRVO by injecting triamcinolone acetonide into the vitreous cavity. Intravitreous injection of triamcinolone acetonide has been shown to have minimal adverse effects in both animal and clinical studies. Triamcinolone acetonide may reduce macular edema, possibly by reducing the breakdown of the blood-retinal barrier, nonspecifically inhibiting the arachidonic acid pathway, or downregulating vascular endothelial growth factor.

Intravitreous triamcinolone acetonide induced a prompt anatomic and functional improvement in our patient with nonischemic CRVO (case 1). The visual acuity of this patient improved from 20/200 to 20/25 in 1 month. Additionally, the thickness of the central fovea, as measured by OCT, was reduced from 600 µm to 100 µm in 1 month.

In the patient with ischemic CRVO (case 2), intravitreous triamcinolone acetonide also appeared to produce significant but temporary anatomic benefit. Visual acuity improvement was noted but was less dramatic than in the patient with nonischemic CRVO. As in the patient with nonischemic CRVO, the central foveal thickness was reduced rapidly and dramatically during 1 month following intravitreous injection. This effect, however, was transient; a decrease in visual acuity and an increase in macular edema occurred 3 months following injection. This may be related to the severity of ischemic CRVO. A single injection of triamcinolone acetonide may remain in the vitreous cavity for up to 3 months following injection. It is possible that 1 injection of intravitreous triamcinolone lasting 3 months in the vitreous cavity may be sufficient treatment for macular edema caused by nonischemic CRVO but not for macular edema caused by ischemic CRVO. A repeated injection might again have reduced the macular edema and improved visual acuity in the patient with ischemic CRVO.

In the absence of a definite role for macular laser photocoagulation in the setting of macular edema from CRVO, intravitreous injection of triamcinolone acetonide may be a viable treatment option. The 2 patients described previously had a prompt anatomic and functional response, although the need for repeated treatment and possible adverse effects should be investigated further. No adverse effects such as retinal detachment, endophthalmitis, cataract, or glaucoma occurred in this series. Further study is warranted to evaluate the safety and efficacy of this promising treatment modality for CRVO complicated by macular edema.

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Intravitreal Antivirals in the Management of Patients With Acquired Immunodeficiency Syndrome With Progressive Outer Retinal Necrosis

Retinal infection with herpes varicella zoster in patients with acquired immunodeficiency syndrome (AIDS) usually produces multifocal outer retinal whitening that rapidly progresses to confluent, full-thickness retinal necrosis. This form of necrotizing herpetic retinopathy, known as progressive outer retinal necrosis, differs from acute retinal necrosis syndrome...
principally in the lack of prominent intraocular inflammation. Treatment with intravenous antiviral therapy alone has been associated with a disappointing visual prognosis. We report the visual outcomes associated with the use of combination systemic and intravitreal antivirals in the management of 7 patients with AIDS with progressive outer retinal necrosis.

**Report of Cases.** There were 4 men and 3 women with AIDS (mean age, 34.6 years [range, 27-38 years]) (Table 1). Two of the 7 patients had a history of cutaneous varicella-zoster virus infection and 1 had encephalitis. Six of 7 patients had bilateral involvement at the time of the diagnosis of retinitis, and the remaining patient developed involvement of the fellow eye within a 2-month period. Median follow-up was 10 months, with a range of 4 to 30 months. All 7 patients demonstrated clinical features consistent with progressive outer retinal necrosis.

Median visual acuity at the time of diagnosis was 20/80 (Table 2). The visual acuity in 8 eyes ranged from 20/20 to 20/80 and 6 eyes were hand motions to no light perception. All patients were able to see at least 20/60 in at least 1 eye. Retinal lesions were present in zone 3 in all 14 eyes: only in zone 3 in 3 eyes (21%); only in zones 3 and 2 in 3 eyes (21%); and in all 3 zones in 8 eyes (57%). No patient had lesions confined to only zones 1 or 2. Three of 7 patients (5 eyes) had retinal detachment at diagnosis, and 3 detachments involved the macula. Of the 9 retinas that were not detached at diagnosis, 5 were treated with a prophylactic demarcating laser. One laser-treated retina subsequently detached. All 4 nondetached retinas that were not treated with the demarcating laser subsequently detached.

All patients received intravenous ganciclovir sodium and foscarnet; 1 patient also received intravenous acyclovir. Two patients (4 eyes) received intravitreal injections of ganciclovir sodium (2 mg/0.05 mL) and foscarnet (1.2 mg/0.05 mL). The remaining 5 patients (7 eyes) received intravitreal injections of ganciclovir sodium (2 mg/0.05 mL). A median of 6 injections (range, 3-15 injections) during 14 days (range, 6-88 days) were given per eye. Two eyes with light perception vision were not injected. One eye with hand motion vision and retinal detachment recovered a visual acuity of 20/80 after injections and retinal detachment repair. Three other eyes with hand motions or worse vision were injected and had poor visual outcomes.

Five (45%) of 11 treated eyes achieved a final visual acuity of 20/80 or better, and only 2 (18%) of the 11 treated eyes progressed to no light perception vision. All patients maintained a visual acuity of 20/400 or better in at least 1 eye. No progression of disease occurred during intravitreal treatment. Recurrent disease occurred in only 1 eye and was treated successfully by resumption of both intravenous and intravitreal ganciclovir and foscarnet therapy.

**Comment.** In the original series of 38 patients with progressive outer retinal necrosis treated with intravenous antivirals alone, 42 (67%) of 63 eyes progressed to no light perception within 4 weeks after diagnosis. A subsequent study of 20 patients with progressive outer retinal necrosis treated with intravenous antivirals reported 19 (49%) of 39 eyes progressing to no light perception within 6 months. The outcomes of patients treated with more than 1 intravenous antiviral agent were statistically better than those who received only a single drug, but only 4 (10%) of 39 eyes achieved a visual acuity of 20/80 or better. In a more recent study of 6 patients with progressive outer retinal necrosis treated with combination intravenous antivirals, a final visual acuity of 20/80 or better was achieved in only 2 (22%) of 9 treated eyes. In contrast, 5 (45%) of the 12 eyes treated with both intravenous and intravitreal antivirals (35% of the 14 total eyes) in the current series had a final visual acuity of 20/80 or better. Five of the 7 eyes with final visual outcomes that were light perception or no light perception had hand motions to no light perception at the time of diagnosis.

Rhegmatogenous retinal detachment also contributes to poor visual outcome and occurred in about 70% of eyes in the prior series, in which most retinas detached after treatment was begun. In the current series, there was a similar total rate of detachments, with 35% detached at the time of diagnosis and 35% detaching subsequently. However, in the current series, 1 (20%) of 5 retinas treated with a demarcating laser subsequently detached compared with 4 (100%) of 4 untreated retinas. The more rapid healing from the use of intravitreal antivirals together with the use of a prophylactic demarcating laser may have contributed to the reduced rate of retinal detachment after treatment was begun.

The limitations of comparing results of the current series with results reported in historical controls should be noted. For instance, the original series of patients was reported soon after the recognition of progressive outer retinal necrosis as a syndrome; earlier recognition and treatment might have improved the prognosis in these eyes. In addition, most patients in the originally reported series were treated with intravenous acyclovir rather than gan-

### Table 1. Patient Demographics and Baseline Data*

<table>
<thead>
<tr>
<th>Patient/Sex/Age, y</th>
<th>Race</th>
<th>Extraocular Manifestations</th>
<th>Duration of Follow-up, mo</th>
</tr>
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<tbody>
<tr>
<td>1/M/38</td>
<td>A</td>
<td>VZV</td>
<td>4</td>
</tr>
<tr>
<td>2/M/38</td>
<td>W</td>
<td>VZV</td>
<td>6</td>
</tr>
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<td>3/M/32</td>
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<td>None</td>
<td>6</td>
</tr>
<tr>
<td>4/F/27</td>
<td>A</td>
<td>VZV</td>
<td>11</td>
</tr>
<tr>
<td>5/F/38</td>
<td>H</td>
<td>VZV</td>
<td>20</td>
</tr>
<tr>
<td>6/F/36</td>
<td>A</td>
<td>None</td>
<td>30</td>
</tr>
<tr>
<td>7/F/53</td>
<td>A</td>
<td>None</td>
<td>10</td>
</tr>
</tbody>
</table>

* A indicates African American; VZV, cutaneous varicella-zoster virus infection; W, white; and H, Hispanic.
ciclovir, foscarnet, or combination systemic antiviral therapy. Moreover, the current use of highly active antiretroviral therapy (HAART) likely influences the prognosis of progressive outer retinal necrosis as it does with cytomegalovirus retinitis. However, in the current series, only 2 patients were being treated with HAART (either because the patients were initially examined before the widespread use of HAART or because of noncompliance with medical therapy). Finally, although the zones of retinal involvement were known for the patients in the current series, the retrospective nature of this study does not permit precise quantification of the baseline extent of disease, which would be necessary, for instance, to accurately assess the efficacy of laser demarcation in preventing retinal detachment.

Published information on visual outcomes following the use of intravitreal antivirals in the management of progressive outer retinal necrosis is limited, consisting of only 3 reports. Three (50%) of 6 involved eyes of the reported 4 patients achieved a final visual acuity of 20/80 or better with intravitreal therapy. Progressive outer retinal necrosis remains rare enough that it is difficult to define optimal treatment. Our preferred regimen for intravitreal treatment is to inject intravitreous ganciclovir sodium (2 mg/0.05 mL) and foscarnet (1.2 mg/0.05 mL) 3 times weekly for 2 weeks, followed by maintenance therapy of injections once or twice per week as indicated until the retinitis is stabilized. Laser photocoagulation to demarcate necrotizing retinitis is applied whenever possible. Because central nervous system involvement can occur in association with necrotizing herpetic retinitis, we also use systemic antiviral therapy. Our preferred regimen is intravenous ganciclovir sodium 5 mg/kg/day (or foscarnet 50 mg/kg/day) by continuous intravenous infusion. Patients with visual field deficits often benefit from treatment with intravitreal ganciclovir and foscarnet when central vision is threatened.

### Table 2. Summary of Treatment and Visual Outcome*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Eye</th>
<th>Initial Visual Acuity</th>
<th>Therapy</th>
<th>No. of Injections</th>
<th>Time Period of Injections, d</th>
<th>Interval Between Initial Examination and RD, mo</th>
<th>Visual Acuity (RD)</th>
<th>Surgery</th>
<th>Complications</th>
<th>Final Visual Acuity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OD</td>
<td>HM</td>
<td>IV ganciclovir sodium and foscarnet, intravitreal ganciclovir and foscarnet (both eyes)</td>
<td>3</td>
<td>6</td>
<td>No</td>
<td>...</td>
<td>...</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>20/60</td>
<td>8</td>
<td>30</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>none</td>
<td>none</td>
<td>20/50</td>
</tr>
<tr>
<td>2</td>
<td>OD</td>
<td>20/25</td>
<td>IV ganciclovir and foscarnet, intravitreal ganciclovir and foscarnet (both eyes)</td>
<td>6</td>
<td>14</td>
<td>No</td>
<td>...</td>
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<td>20/40</td>
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<tr>
<td></td>
<td>OS</td>
<td>20/60</td>
<td>6</td>
<td>14</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>none</td>
<td>none</td>
<td>20/50</td>
</tr>
<tr>
<td>3</td>
<td>OD</td>
<td>HM</td>
<td>IV ganciclovir and foscarnet, intravitreal ganciclovir (both eyes)</td>
<td>9</td>
<td>23</td>
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<td>0</td>
<td>HM</td>
<td>PPV, silicone oil, retinectomy</td>
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<tr>
<td></td>
<td>OS</td>
<td>LP</td>
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<td>LP</td>
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<td>none</td>
<td>LP</td>
</tr>
<tr>
<td>4</td>
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<td>LP</td>
<td>IV acyclovir, ganciclovir, and foscarnet, intravitreal ganciclovir (left eye)</td>
<td>...</td>
<td>...</td>
<td>Yes</td>
<td>0</td>
<td>LP</td>
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<td>20/40</td>
</tr>
<tr>
<td>5</td>
<td>OD</td>
<td>20/20</td>
<td>IV ganciclovir and foscarnet, intravitreal ganciclovir (right eye)</td>
<td>15</td>
<td>72</td>
<td>No</td>
<td>...</td>
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<td>OS</td>
<td>LP</td>
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<td>...</td>
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<td>LP</td>
<td>none</td>
<td>none</td>
<td>NLP</td>
</tr>
<tr>
<td>6</td>
<td>OD</td>
<td>20/80</td>
<td>IV ganciclovir and foscarnet, intravitreal ganciclovir (right eye)</td>
<td>6</td>
<td>20</td>
<td>No</td>
<td>...</td>
<td>...</td>
<td>Cataract extraction/PCIOL</td>
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</tr>
<tr>
<td></td>
<td>OS</td>
<td>20/50</td>
<td>...</td>
<td>...</td>
<td>Yes</td>
<td>3</td>
<td>10/200</td>
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<td>Cataract</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>OD</td>
<td>NLP</td>
<td>IV ganciclovir and foscarnet, intravitreal ganciclovir (both eyes)</td>
<td>5</td>
<td>10</td>
<td>Yes</td>
<td>7</td>
<td>NLP</td>
<td>None</td>
<td>Papillopathy</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>20/60</td>
<td>5</td>
<td>10</td>
<td>No</td>
<td>...</td>
<td>...</td>
<td>none</td>
<td>20/80</td>
<td>NLP</td>
</tr>
</tbody>
</table>

*RD indicates retinal detachment; HM, hand motions; IV, intravenous; NLP, no light perception; PPV, pars plana vitrectomy; LP, light perception; PCIOL, posterior chamber intraocular lens; and ellipses, not applicable.

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ganciclovir or oral valganciclovir at induction doses for 3 weeks and intravenous foscarnet at induction doses for 2 weeks, followed by maintenance antiviral therapy with oral ganciclovir and intravenous foscarnet until complete healing is achieved. A successful transition to oral valganciclovir or valacyclovir can often be made after several weeks of combination antivirals even if there is no improvement in the immune system.

An appropriate control group with which to compare the poor prognosis of progressive outer retinal necrosis treated with intravenous antivirals alone would be necessary to draw definitive conclusions. However, combination systemic and intravitreal antiviral therapy may be associated with improved efficacy in achieving disease resolution, maintaining disease remission, and preserving visual acuity.

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Atypical Retinoblastoma Presentations: A Challenge for the Treating Ophthalmologist

An intraocular procedure in a child with retinoblastoma represents one of the few situations in which an ophthalmologist can produce a disease that may be fatal to the patient. It is always important to consider retinoblastoma, even in children who are atypical in age or appearance for this disease.

Report of Cases. Case 1. A 19-month-old boy with a medical history of malrotation of the intestines who had recently undergone their surgical repair, was referred for evaluation of leukocoria in his right eye. His ocular history was significant for strabismus at 6 months of age that was attributed to prominent epicanthal folds. At approximately 19 months of age, his right eye clearly deviated, and he was referred to a pediatric ophthalmologist who subsequently referred the patient to the oculocerebral unit at the University of California, San Francisco (UCSF).

On examination at UCSF, the patient demonstrated visual fixation that was not central and not steady in the right eye, with central steady and maintained fixation in the patient’s left eye. A 15–prism diop-

Figure 1. Yellow subretinal mass with associated subretinal fluid and scattered subretinal lipids.
The patient was noted as having diffuse ash-leaf spots on dermatologic examination (Figure 2). Infectious serologies for toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus type 1, and herpes simplex virus 2 were negative.

The differential diagnosis included retinal astrocytoma, Coats disease, persistent hyperplastic primary vitreous, or an atypical presentation of retinoblastoma. Subsequent examination of the right eye was remarkable for an intraocular pressure of 53 mm Hg, iris neovascularization, and a total retinal detachment. The right eye was enucleated and replaced with a hydroxyapatite implant. Pathologic examination results revealed necrotic retinoblastoma with a secondary Coats-like response. There was no involvement of the optic nerve. To date, this child has remained free of retinoblastoma in the orbit and in the contralateral eye for 26 months. The patient was referred to a pediatric neurologist for management of tuberous sclerosis with central nervous system involvement. The child remains asymptomatic from this disease process.

Case 2. A previously healthy 6-year-old boy who had undergone an undiagnostic anterior chamber and vitreous tap in Ecuador was referred to UCSF for further consideration of a mass in his right globe. Findings from an extensive workup for infectious disease performed in Ecuador were negative. He had been given a preliminary diagnosis of Coats disease.

He first visited UCSF under a regimen of topical fluorometholone and atropine for his right eye. On examination, his visual acuity was no light perception OD and 20/20 OS. Leukocoria was present in the right eye. Slitlamp examination of his right eye was remarkable for shallow and inferior iridocorneal adhesions, a neovascularized iris, and retinoblastoma recurrence. To date, this child had previously had a drainage procedure and an anterior chamber tap, the UCSF tumor board recommended 6 months of adjuvant chemotherapy. The boy completed 6 cycles of combination carboplatin, etoposide, and vincristine, which he tolerated well. He has relocated to the United States and receives regular follow-up monitoring. To date, after 32 months of follow-up, he continues to be without evidence of retinoblastoma recurrence.

Case 3. A previously healthy 9-year-old girl visited her ophthalmologist with a retinal detachment following trauma to her left eye from a baseball. She was found to have a solid retinal detachment with white flocculent material under the retina and within the vitreous cavity, though she denied having any visual symptoms. A review of family photographs showed evidence of left eye leukocoria lasting for 30 months.

Examination at UCSF demonstrated a visual acuity of 20/20 OD and no light perception OS. Intraocular pressures were 16 mm Hg OD and 20 mm Hg OS. Slitlamp examination showed diffuse rubecosis iriditis in the left eye, as well as snow-white material in the vitreous that aggregated into clumps and was without intrinsic vasculature (Figure 3). A shallow and diffuse retinal detachment was observed posteriorly. On fluorescein angiography, a posterior tumor mass was noted in the left eye, along with vitreous opacities and iris rubecosis. Ultrasonography failed to demonstrate any intrinsic calcification.

During examination while the patient was under anesthesia, neither normal retinal structures nor the optic nerve could be visualized. The vitreous demonstrated a confluent ocular process that had the appearance of inflammation, but that potentially represented vitreous seeding from retinoblastoma.

Computed tomographic scans demonstrated high attenuation of the right vitreous, suggesting that the vitreous was filled with proteinaceous material. Additionally, 2 calcifications were seen within the anterolateral aspect of the globe.

Pathologic inspection revealed diffuse retinoblastoma with an extensive necrotic tumor. Focal areas of calcification invaded the optic nerve but did not extend posterior to the lamina cribrosa. Results of a full metastatic workup were negative; however, since this child had previously had a drainage procedure and an anterior chamber tap, the UCSF tumor board recommended 6 months of adjuvant chemotherapy. The boy completed 6 cycles of combination carboplatin, etoposide, and vincristine, which he tolerated well. He has relocated to the United States and receives regular follow-up monitoring. To date, after 32 months of follow-up, he continues to be without evidence of retinoblastoma recurrence.
out intrinsic calcification and was thought unlikely to be a retinoblastoma, especially in light of the child’s advanced age.

The differential diagnosis included a massive reaction in the vitreous cells to an inflammatory or infectious process vs retinoblastoma. Since the eye was blind as a result of iris neovascularization, an enucleation was performed.

Pathologic inspection revealed necrotic retinoblastoma cells, which spared the choroid but invaded the optic nerve posterior to the lamina cribrosa. Results of a systemic workup for metastasis were negative. The patient’s case was presented to the UCSF tumor board, which recommended adjuvant chemotherapy. She underwent a 6-month course of carboplatin, etoposide, and vincristine, and to date, she has been without recurrence for 16 months.

Comment. Atypical cases of retinoblastoma may lead to diagnostic dilemmas. In the first case, a 19-month-old boy was referred for leukocoria. The diagnosis of retinoblastoma was complicated by magnetic resonance imaging findings consistent with tuberous sclerosis. This made the possibility of an intraocular astrocytic hamartoma likely, since approximately half of all patients with tuberous sclerosis demonstrate retinal hamartomas. Atypical retinal astrocytomas with peculiar neovascularization have been reported. The eye was also judged to be small, involving persistent hyperplastic primary vitreous in the differential diagnosis. The clinical presentation, however, was most consistent with Coats disease, and retinoblastoma with a prominent Coats-like response was confirmed by the pathology report. No evidence of intrinsic calcification was found within this tumor.

In the second case, a 6-year-old boy was referred from Ecuador with a diagnosis of Coats disease. The results of clinical imaging scans at UCSF suggested proteinaceous material within the vitreous and no focal tumor mass. However, the presence of calcification on computed tomographic scans, which could have been consistent with dystrophic calcification in Coats disease, increased suspicion for retinoblastoma. Use of contrast magnetic resonance imaging has increased the sensitivity in distinguishing Coats disease from retinoblastoma.

Enhancement of detached sensory retina with the absence of intraocular enhancement following gadolinium–diethylenetriamine pentaacetic acid (DPTA) treatment favors a diagnosis of Coats disease. Some difficulty remains, however, in differentiating retinoblastoma from advanced Coats disease. Despite the older age at presentation, retinoblastoma was confirmed histopathologically. He unfortunately underwent 6 months of adjuvant chemotherapy because of the procedure that was performed in Ecuador.

In the third case, a 9-year-old girl had a clinical appearance suggestive of uveitis. The cellular material that filled the vitreal space showed no intrinsic calcification and was without intrinsic vascularity. Because the child was 9 years old at the time of examination, retinoblastoma was, again, a relatively low consideration. Although retinoblastoma becomes less frequent with older age, it has been described in adult populations. Should this child have demonstrated effective vision, a vitreous aspirate and biopsy (as recommended by several retina specialists) could have been performed. Children with retinoblastoma undergoing intraocular procedures may require bone marrow transplantation for cure. Even with aggressive treatment, many succumb to disseminated disease once the integrity of the globe has been violated by an intraocular procedure.

In summary, the treating ophthalmologist should retain a high index of suspicion for retinoblastoma in all children with intraocular disease, even those who present with an atypical appearance or at an advanced age. Children with no view of the posterior pole who have histories of trauma and hyphema may harbor occult retinoblastoma. Children with uveitic or Coats-like scenarios may also represent unusual manifestations of this disease. Unless retinoblastoma is considered, improper actions may be undertaken, resulting in a potential increase in morbidity and mortality for patients with this disease.

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2. Jost BF, Olk RJ. Atypical retinitis proliferans, reti-
I

Immunotherapy for Low-Grade Non-Hodgkin Secondary Lymphoma of the Orbit

Lymphoid tumors are the most common primary orbital malignancy. However, they constitute only about 2% of all nodal and extranodal lymphomas. Most published reports advocate the use of external beam radiotherapy or systemic chemotherapy for the treatment of orbital lymphoma. Recent reports have suggested that immunotherapy may also be effective in the treatment of low-grade non-Hodgkin lymphoma (NHL). We describe 4 patients in whom orbital NHL was treated effectively with immunotherapy using anti-CD20 monoclonal antibodies. To our knowledge, there are no previously published reports of monoclonal antibody therapy for NHL of the orbit.

Report of Cases. Between October 1999 and May 2001, 4 patients with the diagnosis of NHL of the orbit were treated at our institution with immunotherapy using monoclonal antibodies to CD20. When initially examined by us, all 4 patients had orbital lymphoma as a secondary extranodal site of involvement of previously diagnosed NHL. For each patient, clinical records and imaging studies were reviewed to establish the diagnosis and document response. Table 1 summarizes the clinical features, histologic classification, immunophenotype, and disease stage at the time of diagnosis of orbital lymphoma for each patient. Table 2 summarizes the staging system used in our series. All 4 patients underwent an orbital biopsy to confirm the diagnosis and the histologic classification of the orbital lymphoma. Patients 1, 2, and 3 received intravenous rituximab (Rituxan; Genentech, Inc, South San Francisco, Calif), 375 mg/m² weekly for 4 weeks. Patient 4 received intravenous rituximab, 250 mg/m², followed approximately 1 week later by a second infusion of rituximab, 250 mg/m², and yttrium-90-labeled (⁹⁰Y) ibritumomab tiuxetan (Zevalin; IDEC Pharmaceuticals Corporation, San Diego, Calif), 0.4 mCi/kg (14.8 MBq/kg).

In all 4 patients, the histologic features of the orbital lesion were similar to the previously established histologic classification of lymphoma. The histologic type in each patient, as confirmed by examination of an orbital biopsy specimen, was considered low grade. All patients had nearly complete resolution of their orbital lymphoma and remained without evidence of orbital disease at most recent follow-up (October 2001). Two patients had progression of lymphoma in other sites and received alternative therapy. The follow-up time after completion of immunotherapy ranged from 6 to 22 months (mean, 14.5 months). Figure 1 shows the orbital mass in patient 3, before and 3 months after completion of treatment with rituximab. Figure 2 shows the orbital lesion in patient 4, before and 2 months after completion of treatment with rituximab and ⁹⁰Y ibritumomab tiuxetan. The only adverse effects reported by the 4 patients were mild neutropenia and thrombocytopenia.

Comment. Monoclonal antibodies can be used to recruit a patient's immune system to target antigens that are expressed on cancer cells. Rituximab is the first monoclonal antibody licensed by the US Food and Drug Administration to treat NHL. Rituximab is a genetically engineered chimeric (murine-human) monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B cells. Multicenter studies have demonstrated its efficacy against relapsed or refractory low-grade, CD20-positive, B-cell follicular NHL. In these trials, up to 60% of patients with follicular lymphomas and a third of patients with diffuse large cell and mantle cell lymphomas achieved objective remissions.

In vitro, rituximab is capable of mediating antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity of CD20-expressing tumor cells. Direct effects have also been observed, including the induction of apoptosis in some B-cell NHL cell lines. In addition, rituximab can sensitize tumor cells to the cytotoxic effects of conventional chemotherapy. Thus,

<table>
<thead>
<tr>
<th>Table 1. Clinical Features of Patients With Orbital Lymphoma Treated With Immunotherapy*</th>
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<tr>
<td>Patient No./Sex/Age, y</td>
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<tr>
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</tr>
<tr>
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<tr>
<td>2/f/68</td>
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<tr>
<td>3/f/83</td>
</tr>
<tr>
<td>4/M/77</td>
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</table>

*All patients had a B-cell immunophenotype and an initial lymphoma stage of IV. †Based on examination of the orbital biopsy specimen.

<table>
<thead>
<tr>
<th>Table 2. Ann Arbor Staging System for Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
</tbody>
</table>
this agent may be a good addition to conventional chemotherapy in cases of refractory NHL. Another advantage of immunotherapy with rituximab is that patients can be treated repetitively, since immune responses occur in fewer than 1% of patients.

A mechanism for improving the potency of rituximab and the survival benefit it confers is to conjugate this monoclonal antibody to a radionuclide ligand. Several potential advantages have been identified that favor the use of radiolabeled antibodies. First, radioimmunoconjugates kill tumor cells primarily by the emission of radioactive particles and therefore may be therapeutically effective, even in hosts with defective immune effector function. Furthermore, the beta particles emitted by the radioligand are tumoricidal over a larger area than just the cell to which the ligand attaches, allowing for elimination of antigen-negative tumor cells by radioactive “cross fire” from neighboring antigen-positive, antibody-coated cells. Yttrium 90–labeled ibritumomab tiuxetan is one such radiolabeled monoclonal antibody.

Yttrium 90–labeled ibritumomab tiuxetan is a unique compound composed of a murine monoclonal antibody (ibritumomab), the linker-chelator tiuxetan, and the radioisotope 90Y, which is securely chelated via the linker. Like its unlabeled chimeric counterpart, rituximab, 90Y ibritumomab tiuxetan targets the CD20 antigen, which is present on 95% of B-cell lymphomas. Yttrium 90–labeled anti-CD20 antibodies have been associated with response rates of 70% to 80% in the treatment of NHL.
Since most primary and secondary orbital lymphomas are thought to be low-grade B-cell NHL, the use of rituximab or its radiolabeled counterpart, \(^{90}\)Y ibritumomab tiuxetan, as an alternative treatment modality for orbital lymphomas is intriguing. Targeted immunotherapy may offer several advantages over conventional chemotherapy or external beam radiotherapy in the treatment of orbital lymphomas, including fewer adverse effects and the potential for repeated treatments.

The toxicity of rituximab in patients with NHL has been considerably less than that of traditional chemotherapy; in most patients, rituximab causes no significant alopecia, nausea, or myelosuppression. Common symptoms observed with the initial monoclonal antibody infusion include fever, chills, mild throat irritation, rash, and, rarely, rigors. In general, treatment with rituximab is well tolerated. Fewer than 10% of patients develop more serious symptoms such as bronchospasm or hypotension. The more serious adverse effects of rituximab are observed in patients with high levels of malignant B cells circulating in the peripheral blood. For most patients, controlled administration of the initial infusion by starting at a low dose, with premedication using acetaminophen and diphenhydramine hydrochloride and a slow rate escalation, results in minimal adverse effects. After completion of rituximab therapy, which typically lasts 1 month, long-term complications are unusual. The most common long-term adverse effect is B-cell depletion, which can last 6 to 9 months.

Rituximab should also produce fewer adverse effects than external beam radiotherapy, which has been associated with ocular adverse effects such as superficial keratopathy, dry eye syndrome, cataract formation, radiation retinopathy, and neovascular glaucoma. Whether treatment of orbital lymphoma with a radiolabeled monoclonal antibody such as \(^{90}\)Y ibritumomab tiuxetan is associated with fewer radiation-induced ocular adverse effects compared with external beam radiotherapy remains to be determined. According to the results of most dosimetry studies, the median estimated radiation dose absorbed by various organs after administration of the radiolabeled antibody \(^{90}\)Y ibritumomab tiuxetan ranges from 38 to 340 rad (0.38-3.40 Gy). The median estimated radiation dose absorbed by the tumor is 1700 rad. In contrast, the median total dose of radiation from external beam radiotherapy for NHL of the orbit is 4000 rad (40 Gy) (range, 2000-5000 rad [20-50 Gy]).

Our small case series provides limited evidence that rituximab or \(^{90}\)Y ibritumomab tiuxetan can be used effectively and safely for low-grade B-cell NHL affecting the orbit. Larger studies are required to study the efficacy of monoclonal antibody treatment for orbital lymphomas and to compare the toxicity profile of immunotherapy with that of other, more conventional forms of therapy, such as external beam radiotherapy and chemotherapy.

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