study of the heart.11 These findings raise new questions regarding the mechanisms of the disease.

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However, these tumors can occasionally result in severe vision loss. One such case is described herein with the unusual associated symptom of sound-induced phosphenes.

Report of a Case. A 54-year-old white man sought care because of 5 months of blurred vision and decreased peripheral vision in the left eye. He was found to have a pigmented lesion on the left optic nerve and referred for further evaluation. He had no history of eye disease and his medical history was noncontributory.

On examination, his visual acuity was 20/20 OD and 20/32 OS. The pupils were symmetrical with no afferent pupillary defect. Intraocular pressures were 20 mm Hg OD and 21 mm Hg OS. There was no ocular melanocytosis. The right fundus appeared normal. A 2.5 x 2.0-mm-darkly pigmented lesion obscured most of the left optic disc (Figure 1A). The lesion height was determined to be 1.2 mm by ultrasonography (Figure 2A). Fluorescein angiography demonstrated hypofluorescence in the area of the lesion, with late staining of the visible portion of the optic nerve head (Figure 3). Automated perimetry showed an inferior field defect in the left eye. The presumptive diagnosis was melanocytoma of the optic disc and observation was recommended.

Approximately 9 months after the initial examination, the patient noted a further decrease in vision in his left eye, pain behind the eye, and flashes of light on hearing a loud noise (sound-induced phosphenes) when in the dark. Examination demonstrated a visual acuity of 20/25 OD and 20/50 OS. There was a left afferent pupillary defect. Fundus examination of the left eye showed no significant change in the size of the lesion (Figure 1B). Ultrasonography demonstrated that the lesion’s height had increased to 1.6 mm (Figure 2B). Goldmann perimetry showed severe constriction and an inferior field defect in the left eye. Magnetic resonance imaging showed an enhancing lesion of the optic nerve, which appeared bright on T1-weighted images (Figure 4). The nerve posterior to the lesion appeared to be atrophic. Fluorescein angiography demonstrated no significant change since the initial examination (Figure 2B).

Eighteen months after the initial examination, the patient returned with further decrease in vision of the left eye to light perception. Fundus examination showed no change in the appearance of the melanocytoma (Figure 1C). Some peripheral retinal hemorrhages were noted. The height of the tumor remained at 1.6 mm when measured by ultrasonography. Seven months later, the patient had lost light perception in his left eye, and diffuse retinal hemorrhages were evident throughout the fundus with dilated and tortuous veins, consistent with a central retinal vein occlusion (Figure 1D). The height of the mass remained stable as determined by results of ultrasonography. Over the next 5 months, the patient developed neovascular glaucoma and, despite panretinal photoagulation, the eye was enucleated because of pain. The sound-induced phosphenes persisted for up to 16 months after enucleation but decreased in frequency.

Gross pathologic examination of the enucleated eye revealed a 25 x 25 x 25-mm globe with 2 mm of optic nerve attached. Light microscopic examination showed partial closure of the anterior segment angle with peripheral anterior synechiae. A neovascular membrane was noted on the anterior surface of the iris with associated ectropion uveae. There were numerous hemorrhages throughout all retinal layers. Pigment-laden macrophages were noted in the subretinal space with some migration into the neural retina. The ganglion cell layer was attenuated. A heavily pigmented tumor occupied most of the anterior optic nerve (Figure 5A and B). Bleached sections showed small nuclei without prominent nucleoli (Figure 5C). No mitoses were seen. A large area of the retrolaminar portion of the tumor appeared to be necrotic. Proteinaceous debris was observed within a larger caliber venule, indicative of stasis (Figure 5D and F). A thrombus was noted in a vessel likely to be the central retinal artery with evidence of recanalization (Figure 5E). The optic nerve adjacent to the tumor was severely atrophic.

Comment. Melanocytoma of the optic disc is now commonly recog-
nized as a benign tumor of the optic nerve head composed of darkly pigmented plump, polyhedral cells similar to those seen in ocular melanocytosis. The lesion is most often asymptomatic and detected on routine eye examination. Most remain stable in size. Occasionally, melanocytomas can cause significant visual loss, as demonstrated in this case. Spencer proposed that visual field loss associated with melanocytomas

Figure 1. Fundus photographs showing a darkly pigmented lesion of the left optic nerve head. A, Lesion at initial examination. B, Same lesion 9 months later, when vision decreased to 20/50 OS. C, Appearance of the tumor 18 months after initial examination, with further decline in vision to light perception. D, Central retinal vein occlusion was noted 25 months after the initial examination.

Figure 2. Results of B-scan ultrasonography. A, The lesion at the optic nerve head is evident at the initial examination. B, Nine months later, the lesion is slightly more elevated. The retrolaminar portion of the optic nerve also appears enlarged.
resulted from compression of the axons in the optic nerve head and demonstrated histologic evidence of swollen axons adjacent to the tumor. In an evaluation of 20 patients with melanocytoma of the optic disc, evidence of nerve fiber bundle visual field defects were found in 10 (50%), the majority of whom had an afferent pupillary defect. Although visual field loss may be relatively common, acute severe visual loss resulting from a melanocytoma is unusual. A few such cases have been reported in the literature. Shields and colleagues described a case in which a large, necrotic melanocytoma caused occlusion of the central retinal artery and vein. Croxatto et al observed a patient in whom a partially necrotic optic nerve melanocytoma was associated with vaso-occlusive disease of the central retinal artery and branches within the tumor, resulting in ischemic retinopathy and neovascular glaucoma. In a similar case of sudden visual loss related to a melanocytoma of the optic disc, Zimmerman found obstruction of a large retrolaminar branch of the central retinal artery that led to ischemic necrosis of the tumor and optic nerve head. Disc edema and visual loss were the initial signs in the patient described by Zimmerman and in another case reported by Takahashi et al. The intraneural melanocytoma in both cases was initially obscured and became evident only on subsequent follow-up.

The longitudinal observation of our patient demonstrates a spectrum of visual complications related to melanocytoma of the optic nerve. He initially developed evidence of optic neuropathy likely related to compression by the tumor of axons within the optic nerve. Worsening of the optic neuropathy corresponded to growth of the tumor as detected by ultrasonography. The precipitous decline in vision that followed may have resulted from ischemic infarction of the optic nerve or occlusion of the central retinal artery caused by enlargement of the tumor within the optic nerve sheath. The histologic finding of thrombus in what was likely the central retinal artery suggests that arteriolar occlusion was the cause of the marked visual loss in our patient. However, the presence of extensive tumor necrosis, as seen in similar cases, suggests microvascular compromise. The hemodynamic alterations eventually resulted in central retinal vein occlusion with subsequent neovascular glaucoma and loss of the eye.

To our knowledge, the symptom of sound-induced phosphenes has not been previously reported in association with melanocytoma. Various instances of patients noting flashes of light triggered by auditory stimuli
have been described, primarily in patients with optic nerve disease. In most cases, the phenomenon occurred in the dark as the patient was resting or preparing to sleep. The mechanism underlying this symptom is unclear, but it has been proposed that under conditions of reduced visual stimulation, neurons in the brain capable of responding to both visual and auditory signals may become unusually sensitive to sounds. The persistence of the phosphenes in this patient after enucleation supports a central rather than ocular cause for the flashes.

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Ocular Adverse Effects Associated With Cyclooxygenase-2 Inhibitors

An important event in the treatment of inflammatory disease was the identification of selective inhibitors of cyclooxygenase-2 (COX-2). Cyclooxygenase-1 (COX-1) inhibitors are responsible for many of the adverse effects of nonsteroidal anti-inflammatory drugs, such as gastrointestinal disturbances, while blockade of COX-2 mediates the anti-inflammatory activity with fewer adverse effects. Selective COX-2 inhibitors include rofecoxib (Vioxx; Merck & Co, West Point, Pa), celecoxib (Celebrex; Pfizer Inc, New York, NY), valdecoxib (Bextra; Pfizer Inc), and lumiracoxib (Prexige; Novartis Pharmaceuticals Corp, Basel, Switzerland). Nimesulide (Ainex; Schering-Plough, Santiago, Chile) (and other trade names), and etodolac (Lodine; Wyeth, Madison, NJ) also exhibit selective COX-2 inhibition and can be included in this class of medication which is used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, and dysmenorrhea.1 Nimesulide and lumiracoxib are not approved by the Food and Drug Administration and are not marketed in the United States and Merck removed Vioxx from the market worldwide in September 2004 because of a possible increased risk of heart attack and stroke.

From the literature, there are 8 case reports of visual disturbance from treatment with COX-2 inhibitors.2,3 These include orange spots in vision while taking celecoxib, temporary blindness from rofecoxib, a jellybean-like area of vision loss centrally from celecoxib, and 5 cases of blurred vision (4 cases related to celecoxib and 1 related to rofecoxib). The visual disturbances all resolved within 72 hours of discontinuing the drug (positive dechallenge), however no rechallenge data (that the adverse reaction reoccurred when restarting the drug) is available.

Recently, a large number of inquiries and case reports were submitted to the National Registry of Drug-Induced Ocular Side Effects (www.eyedrugregistry.com) associating COX-2 inhibitors and visual adverse effects, prompting an examination of this first large series of spontaneous reports of possible adverse visual effects secondary to COX-2 inhibitors. The possible etiologies of the adverse ocular reactions are explored.

Methods. A total of 1006 reports were collected at the National Registry of Drug-Induced Ocular Side Effects (Casey Eye Institute, Portland, Ore). Spontaneous case reports from the National Registry, the Food and Drug Administration, and the World Health Organization were analyzed. The main information in the report from ophthalmologists includes the type of COX-2 inhibitor, age, sex, dosage, duration of therapy, concomitant therapies, and type of ocular adverse effect. Special attention was paid to reports with positive dechallenge and positive rechallenge, given that this information is the most compelling for a cause-and-effect relationship with COX-2 inhibitors causing a visual adverse effect.4 Spontaneous reports originated from the countries where the medications are marketed. Blurred vision and conjunctivitis were the majority of these types of reports and, therefore, are the focus of the results.

Results. Celecoxib. There were 238 reported cases of blurred vision from celecoxib, with 67 positive dechallenge and 15 positive rechallenge reports. There were also 71 case reports of conjunctivitis due to celecoxib, with 12 positive dechallenge and 4 positive rechallenge reports. Average age was 58 years (range, 43-81 years) receiving standard doses (200 mg/d) with an average duration of therapy of 48 days. Three subjects also received diazepam in addition to celecoxib (1 conjunctivitis, 2 blurred vision).

Rofecoxib. A total of 258 reports of blurred vision from rofecoxib were collected, with 48 positive dechallenge and 21 positive rechallenge reports. There were 85 cases of conjunctivitis due to rofecoxib, with 18 positive dechallenge and 4 positive rechallenge reports. Average age was 62 years (range, 36-85 years) receiving standard doses (12.5-25 mg/d) with an average duration of therapy of 76 days. Two subjects with blurred vision were also taking levothyroxine and experienced visual hallucinations with positive dechallenge and positive rechallenge.

Valdecoxib. There were 14 case reports of blurred vision secondary to valdecoxib, with 3 positive dechallenge reports and 1 positive rechallenge report. There were also 14 case reports of conjunctivitis due to valdecoxib, with 1 positive dechallenge report and 1 positive rechallenge report. Average age was 60 years (range, 45-76 years) receiving standard doses (10 mg/d) with an average duration of therapy of 35 days.

Etodolac. Forty-eight case reports of blurred vision secondary to...