Human Subconjunctival Infection of Macacanema formosana: The First Case of Human Infection Reported Worldwide

In the last few decades, the apparently more frequent occurrence of zoonotic helminth infections in man have attracted the attention of parasitologists.1 In particular have been those brought about by the genus Dirofilaria, which has been reported to cause more than 900 cases of human infection. Most of them were due to Dirofilaria repens and Dirofilaria immitis. Therefore, it is worth reporting on a recent human case caused by Macacanema formosana, a filarial parasite of the catarhine monkeys (Macaca cyclops), that came to our attention and apparently has never been reported in humans.

Report of a Case. The patient was a 19-year-old woman who had been living in an urban area of northern Taiwan since childhood. She visited the Department of Ophthalmology, Taipei Veterans General Hospital in November 1999 owing to sudden pain and redness in her left eye. Mild swelling of the left lower eyelid was noted for 1 month and several episodes of severe left periorbital pain happened within these few months. She had never traveled outside Taiwan and never had animals as pets. Her family had a routine annual picnic at the riverside of the Hsin-Tien Shi in northern Taiwan until 3 years previously. She could not recall any unusual insect bite or any contact with monkeys during these picnics.

Complete ophthalmologic examination was performed. Best-corrected visual acuity was 6/4 OU with Snellen distance chart. Slit-lamp examination disclosed a subconjunctival active worm at the nasal side of her left eye with marked conjunctival congestion (Figure 1). Indirect ophthalmoscopic examination revealed a normal fundus. Findings on examination of the right eye were unremarkable. The results of blood and biochemical tests, including the eosinophil count, were normal. No microfilaria was found in blood and urine samples. No lesion was seen on chest radiographs or brain computed tomographic scans.

Under local anesthesia, the conjunctiva was incised and dissected. The worm was removed alive and intact and preserved in 5% formaldehyde for identification. Histologi-
cal sections were prepared for further study of the parasite. Periorbital pain and conjunctival congestion resolved after the surgery. There was no sign of recurrent infection after 2 years’ follow-up.

Parasitologic Findings. The parasite was sent to the Department of Public Veterinary Health and Animal Pathology, University of Bologna, Bologna, Italy, and the Department of Tropical Medicine, Tulane University Medical Center, New Orleans, La, for identification. It was later sent to the Museum of Natural History, Paris, France, for further confirmation of the identity. It was threadlike and approximately 7.5 cm long with a maximum diameter of 510 µm (Figure 2). The anterior extremity (Figure 3) was subconical with a small, round oral opening without lips and surrounded by 2 pairs of circumoral papillae. The cuticle was thin with fine transverse striations. The tail (Figure 4) was short with 2 spicules of unequal length. The longer one (on the worm’s left side) measured 512 µm and the shorter (on the worm’s right side) one, partially protruding from the cloaca, was about 120 µm long. There was a row of approximately 7 caudal papillae, asymmetrically arranged, on either side of the cloaca.

The esophagus could be visualized through the semitransparent body wall. It was divided into a short muscular portion and a much longer glandular portion. The lateral chords contained dark, granular material that could be seen throughout the length of the chords (Figure 5). In the transverse section of the worm (Figure 6), the multilayered structure of the cuticle was evident as was the underlying thin hypodermis. The large lateral chords displayed clusters of pigmented granules that were scattered in the hypodermis as well. The muscle cells were coelomyarian and numerous in each quadrant of the body. The pseudocoel was virtually filled with the large genital tube packed with developing spermatozoa (spermatoocytes). The digestive tube was small and round and lined with a relatively thick endothelium. On the basis of these morphological characteristics, the nematode can be identified as an adult male of Macacanema formosana (Nematoda, Onchocercidae, Dirofilariinae). The morphological characteristics to differentiate M. formosana from other nematodes (Filariaoidae, Ascaridoidea, Oxyuroidea, Strongylida, Spirurida, Rhabditida, and Trichinellidae) were well described by Orihel and Ash.1 Schad and Anderson2 had reported the differential diagnosis of M. formosana with other Onchocercidae, in particular with Edesonfilaria malayensis, the nematode most similar to M. formosana.

Comment. Macacanema formosana was first identified and described by Schad and Anderson in 1963.2 It was a nematode of new genus and species of the family Onchocercidae, subfamily Dirofilariinae. They found the filaria in the peritracheal tissue and diaphragm of Macaca cyclopis, a monkey native to Formosa (Taiwan). Like all filariae, the microfilariae were found in the blood of the host. Little was known about this parasite except for a report published in 1968 by Bergner and Jachowski.3 They found the parasite in the peritracheal and mandibular intermuscular connective tissue.
sues. There was no subconjunctival infection reported in the monkey. The prevalence rate of *M formosana* in the Taiwanese monkey was reported to be as high as 42% in northern Taiwan where the patient had picnicked. *Culicoides* (Insecta, Diptera, Ceratopogonidae), a cosmopolitan genus of biting midges often causing great annoyance to man and animals, was proposed as the most probable transmitting vector of the parasite. Many species of *Culicoides* were identified in northern Taiwan. This large reservoir of the parasite and the existence of the vectors made human infection possible. To our knowledge, this is the first case of human infection caused by *M formosana* to be reported worldwide. However, other cases in the same area may have taken place, but unobserved, as seemed to happen with *D repens* in endemic zones. The prepatent period of the worm has not yet been determined. Based on the size of the worm, the patient would have been infected for at least 1 year and symptoms appeared only after the worm migrated into the subconjunctival space. The reported human *Dirofilaria* infections usually consisted of a single worm, and treatment for the soreness consisted of the worm’s surgical removal. There was no evidence of recurrent infection in our patient after 2 years’ follow-up.

Cases of subconjunctival *D repens* infection occur widely throughout European, African, Middle Eastern, and Asian countries. However, it has never been reported in Taiwan. From the cases reported and our observation, subconjunctival *D repens* and *M formosana* infections shared the characteristics of sudden onset and were treated solely by surgical removal of the worm. From the size of the worms recovered, they might have been migrating in subcutaneous space for a period of time and caused symptoms only when they appeared in the subconjunctiva. The episodic periorbital pain preceding subconjunctival infection in our patient could be caused by the worm’s migration within this area.

The presence of brownish granules in the lateral chords is a phenomenon that has been observed on other occasions both in other nematodes, such as *Mansonella perstans* and *Edesonfilaria* species, and in the same *M formosana*. Their origin is obscure and further studies are necessary to understand their nature. This is, to our knowledge, the first case report of human infection caused by *M formosana* although other cases may have gone by unobserved or unidentified. Since the Taiwan monkeys (*Macaca cyclopis*) have been largely involved in laboratory studies and have close contact with human beings, possible zoonotic infection should be kept in mind.

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Figure 5. The detail of a segment of *Macacanema formosana* where the scattered brownish granules within the lateral chords (L) can be seen (original magnification ×60).

Figure 6. The transverse section of the nematode (partial). C indicates cuticle; I, intestine; M, muscular fibers; T, testicle; and arrowheads, brownish granules in the lateral chord (trichrome-Masson-Goldner stain, original magnification ×250).
Merkel Cell Carcinoma of the Eyelid With a Positive Sentinel Node

Merkel cell carcinoma (MCC) of the eyelid is a rare but aggressive malignancy that metastasizes early to regional lymph nodes. Most clinical series suggest a rate of regional nodal involvement between 21% and 66%. Early detection of occult regional nodal disease may allow for early institution of adjuvant therapy. We describe a patient with MCC of the eyelid with clinically uninvolved nodes who underwent sentinel lymph node (SLN) biopsy soon after the diagnosis of his primary tumor. An SLN was identified and showed histologic evidence of MCC. To our knowledge, this is the first reported case of a positive SLN secondary to MCC of the eyelid.

Report of a Case. A 61-year-old man noted an erythematous lesion on his left upper eyelid in May 2001. He went to his local ophthalmologist, who excised the lesion but did not examine it histologically. In June 2001, the lesion recurred. The recurrent lesion measured approximately 12 mm in diameter. The patient sought an opinion from an ocuoplasty surgeon, who performed a wide local excision of the lesion with frozen section control of the margins. The histologic findings were consistent with MCC of the eyelid (Figure, A and B). Sentinel lymph node biopsy was scheduled but had to be delayed because the patient developed acute appendicitis, necessitating an emergent appendectomy. In July 2001, the patient underwent SLN biopsy using a combination of isosulfan blue dye and Tc 99m-labeled sulfur colloid. The afferent lymphatics were identified before surgery using radio-nucleotide imaging. Intraoperatively, a combination of radiolabeled sulfur colloid and isosulfan blue dye was used to identify SLNs. An area of focal radioactive uptake was identified in the left preauricular (parotid) area using a handheld gamma probe and was marked on the skin. The corresponding SLN was removed and analyzed histologically using serial sectioning and immunohistochemical staining. The node was found to be positive for MCC (Figure, C and D). The patient subsequently underwent a total parotidectomy and completion neck dissection. The parotidectomy specimen included 1 additional lymph node that was positive for MCC. The node was located in the deep lobe of the left parotid gland and showed extracapsular extension.

In September 2001, the patient self-referred to the University of Texas M. D. Anderson Cancer Center (Houston) for further management of his tumor. At this time, he had a well-healed area of excision in his left upper eyelid, and the area of the neck dissection and parotidectomy had healed. Findings on the patient’s ophthalmologic examination were essentially normal, with no clinical evidence of local or regional recurrence of cancer. His systemic workup, including computed tomography of the head and neck, abdomen, and pelvis, chest radiography, and magnetic resonance imaging of the brain, was negative for tumor. A multidisciplinary team, including an ophthalmic surgeon, a head and neck oncologist, and a head and neck radiation oncologist examined the patient and recommended that he receive adjuvant external beam radiation therapy to the eyelid, parotid nodes, and deeper cervical nodes. The team also recommended that the patient be given 4 courses of chemotherapy with etoposide and cisplatin after the completion of radiation therapy.

Comment. In patients with MCC, the regional lymph nodes are thought to be the most common and earliest site of metastasis; thus, adjuvant treatment of the regional lymph nodes has been advocated by many investigators. Jean et al successfully identified 1 or more SLNs in 19 of 20 patients with stage I MCC who underwent SLN biopsy at the time of initial wide local excision. The authors found that 5 (26%) of the 19 patients in whom SLNs were successfully identified had at least 1 histologically positive SLN. Other isolated cases of SLN biopsy for MCC have also been reported. Merkel cell carcinoma of the eyelid is thought to account for 10% of all cases of MCC. In a review of all previously reported cases of MCC of the eyelid, Kivela and Tarkkanen concluded that up to two thirds of patients eventually develop regional nodal involvement. This rate is higher than the rate reported in most single series of MCC of the eyelid. In the largest single series to date, Peters et al reported clinical regional nodal involvement in 3 (21%) of their 14 patients.

Sentinel lymph node biopsy allows for early detection of occult re-

Regional lymph node metastasis and thus, more accurate staging of MCC and the possible institution of early adjuvant therapy. Although SLN biopsy has recently become the standard of care for most solid tumors throughout the body, SLN biopsy in the periocular area remains investigational. To our knowledge, there have been only 2 previous reports of application of SLN biopsy techniques for conjunctival and periorcular tumors. We described successful identification of SLNs in a single patient with a conjunctival melanoma, using a combination of radiolabeled sulfur colloid and isosulfan blue dye. Wilson et al attempted identification of SLNs in 5 patients with periorcular tumors (2 melanomas, 2 meibomian gland carcinomas, and 1 case of mucoepidermoid carcinoma), using radiolabeled sulfur colloid alone. These authors reported successful identification of at least 1 SLN in 5 patients, although the technique used in the latter report is believed by some investigators not likely to lead to the correct identification of the sentinel nodes. Neither of the 2 previous reports of SLN biopsy for conjunctival and periorcular tumors found a positive SLN. To our knowledge, ours is the first reported case in which an SLN was successfully identified in a patient with an eyelid tumor and was also found to be histologically positive. This case underscores the feasibility and potential usefulness of SLN biopsy as a method for identifying occult metastatic disease from an MCC of the eyelid. Early detection of micrometastasis in the regional nodes allows for immediate institution of adjuvant therapy, which may include completion neck dissection, external beam radiation therapy, and adjuvant chemotherapy.

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The Effect of Transpupillary Thermotherapy on the Human Macula

Transpupillary thermotherapy (TTT) was introduced by investigators from the Netherlands in 1995 as an alternative treatment for choroidal melanoma. Since that time, TTT has been used to treat small choroidal melanomas, and preliminary results indicating that TTT can control small melanomas with follow-up of 3 or more years have been published. However, localized retinal destruction, vascular occlusions, and nerve fiber bundle defects are commonly associated with effective treatment of small melanomas with TTT. Despite these observed retinal complications, some investigators have recently reported that TTT, using the same laser intensity to treat choroidal melanoma, may successfully treat occult subfoveal choroidal neovascularizations in patients with age-related macular degeneration without observing deleterious retinal complications. The encouraging results in pilot studies with TTT in the management of occult choroidal neovascular membranes has led to the development of a multicenter prospective randomized clinical trial (Transpupillary Thermotherapy [TTT] of Occult Subfoveal Choroidal Neovascularization in Patients With Age-Related Macular Degeneration Trial) in which patients with subfoveal choroidal neovascular membranes are randomized to a sham treatment or a treatment with a single 60-second exposure of infrared light from the diode laser (810 nm) using a beam diameter of 3 mm and 800 mW of power (Elias Reichel, MD, oral and written communication, January 12, 2000). The unique opportunity afforded by a patient scheduled for enucleation for a malignant melanoma located in the nasal choroid led to this experiment in which infrared light from a diode laser was directed to the macula through a contact lens using the variables identical to those recommended in the TTT of Occult Subfoveal Choroidal Neovascularization in Patients With Age-Related Macular Degeneration Trial. Report of a Case. A 65-year-old woman was referred to the Department of Ophthalmology of the Mayo Clinic, Rochester, Minn, on March 8, 2000, because of a growing pigmented choroidal lesion in the left eye that had been observed to increase in thickness from 2.3 to greater than 4 mm during an interval of 9 years. The visual acuity was 20/20 OD and 20/25+3 OS. The right eye was normal. Results of examination of the left eye showed a normal anterior segment and a pigmented, elevated choroidal lesion, measuring 9 × 9 mm in base dimension, located approximately 4 mm superfornasal to the disc (Figure 1). The ultrasonographic studies demonstrated a solid, dome-shaped tumor (B-scan) with low internal reflectivity (A-scan) consistent with the diagnosis of melanoma. The thickness of the lesion was 4.4 mm. A subretinal fibrotic plaque overlying the central portion of the tumor and a secondary retinal detachment overlying the nasal portion of the tumor were seen. Subretinal fluid extended approximately 1 disc diameter beyond the nasal periphery of the mass. Small accumulations of exudates at the nasal boundary of the tumor were also seen. The retina in the central macular region appeared subtly thickened on biomicroscopy findings. The diagnosis of actively growing malignant melanoma was made, and definitive therapy was recommended. Therapeutic options were
discussed. Brachytherapy was encouraged, but the patient was concerned about the potential for continuing problems with the eye and strongly desired an enucleation. We obtained institutional review board approval for the experiment. The patient was fully informed regarding the use of infrared laser light in the management of macular disease and the possibility that the treatment could cause an alteration of the pigment epithelium and retina overlying the choroidal target tissue. She agreed to have her retina exposed to light from the infrared laser for 60 seconds using 800 mW of power. The laser beam was delivered to the posterior pole through a standard fundus contact lens (Carl Zeiss, Inc, Thornwood, NY), exposing the macula to light from the infrared laser for 60 seconds. Visual acuity was measured with a standard Snellen chart, and the central field was evaluated with an Amsler grid 3 minutes after light exposure. Five days after laser exposure, we re-examined the eye. Best corrected visual acuity was determined, and the central visual field was evaluated with an Amsler grid. Biomicroscopy and ophthalmoscopy were performed, and the appearance of the posterior pole was documented with color fundus photography and fluorescein angiography. The eye was enucleated approximately 3 hours later and fixed in a 0.1M phosphate-buffered solution containing 4% paraformaldehyde and 1% glutaraldehyde. The retina and choroid in the macula were dissected en bloc, fixed in solution, and embedded for transmission electron microscopy. Light microscopy of this region was not performed. The remaining tissue was examined by means of light microscopy.

**Histopathologic Findings.** Color photographs of the macular region showed no obvious abnormality (Figure 2A). The pretreatment fluorescein angiogram showed an early pattern of complex vascular loops within the tumor and patchy leakage of dye from these sites leading to early patchy tissue staining of the tumor. Later frames showed diffuse staining of the retina overlying the tumor. Dye leakage from fluorescein-incompetent capillaries in the perifoveal region was seen, which produced an incomplete pattern of cystoid edema visible in the late frames of the study and arclike areas of diffuse intraretinal staining su-

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**Figure 2.** Prelaser exposure. A, Color fundus photograph of posterior pole showing a normal-appearing macular region. B, Early arteriovenous phase during fluorescein angiography. C, Arteriovenous phase during fluorescein angiography showing subtle hyperfluorescence in the posterior pole and early cystoid edema. D, Recirculation phase showing patchy diffuse intraretinal dye staining and pattern of sector cystoid macular edema.
perior to the fovea, temporal to the fovea, and to a lesser extent inferotemporal to the fovea (Figure 2B-D). The largest dimension of the staining site had a diameter of approximately 3 mm (before and after laser exposure).

During and immediately after transpupillary exposure of the macula to light from the infrared laser, no discernible alteration in the ophthalmoscopic appearance of the fundus was seen. Three minutes after light exposure, the patient noticed a bluish discoloration in the central field of vision that she outlined on the Amsler grid. The best-corrected distance visual acuity 3 minutes after light exposure was 20/100. When the patient returned 5 days later, the central visual acuity had recovered to the pretreatment level (20/25), but she still recognized a faint bluish discoloration in the central part of her vision on Amsler grid testing. She reported that this dyschromatopsia had been decreasing in intensity each day since the exposure. Examination of the fundus 5 days after laser exposure showed no discernible change in the appearance of the fundus. The fluorescein angiogram at the 5-day follow-up visit demonstrated findings identical to those seen in the pretreatment angiogram (Figure 3).

Light microscopy of the enucleated eye showed a malignant melanoma located in the posterior choroid, nasal to the optic disc, that formed a mass measuring 10 × 10 × 3 mm and consisted predominantly of epithelioid cells. A serous detachment of the sensory retina was seen overlying the nasal portion of the tumor. A plaque of fibrous tissue was visible over the central portion of the tumor, and cystoid degeneration was present in the overlying retina (Figure 4A and B).

Results of the ultrastructural examination of the macular and paramacular region, which had been dissected and embedded for transmission electron microscopy, showed retinal pigment epithelial cells with numerous cytoplasmic granules of lipofuscin and melanofuscin with round and irregular shapes rather than the usual oval-shaped melanosome granules (Figure 4C). Focal disruption of cellular membranes and dispersion of pigment granules among outer segments of photoreceptor cells were seen. Vacuolation and distension of the outer segments of the photoreceptors were also observed, with partial disintegration of the lamellar structure with a rare thumbnail-like configuration (Figure 4D). The underlying choriocapillaris showed congestion, but the vessels were normal, with intact walls and normal endothelial cells. The larger choroidal vessels also appeared normal (Figure 4E).

Comment. Transpupillary thermotherapy has been used in recent years as a therapeutic alternative in the management of some choroidal melanomas.1-4 We have shown that effective treatment of selected small choroidal melanomas almost always leads to a profound field defect because of destruction of the photoreceptors and nerve fibers in the retina overlying the treated tu-

Figure 3. Five days after infrared laser exposure. A, Color fundus photographs 5 days after 60-second infrared laser exposure of the macula to a 3-mm beam of infrared light from the diode laser using 800 mW of power. B, Arteriovenous phase during fluorescein angiography showing subtle hyperfluorescence in posterior pole and early sector cystoid edema. C, Recirculation phase showing diffuse intraretinal dye leakage and sector cystoid macular edema. The findings are unchanged from those documented in Figure 2.
When used for treatment of a choroidal melanoma, the same variables recommended by the ongoing multicenter randomized study of occult choroidal neovascular membranes in age-related macular degeneration (800 mW, 60 seconds of exposure, and 3-mm beam diameter) are usually associated with ex-
tensive retinal damage, causing a localized scotoma and, frequently, a wedge-shaped field defect as a result of nerve fiber bundle destruction. Therefore, some concern exists that these variables have been chosen for treatment of choroidal neovascular membranes. Our patient with a malignant melanoma located in the nasal choroid, scheduled for enucleation, consented to have her macula exposed to light from the diode laser using the variables cited above. In this patient’s affected eye, subtle intraretinal edema involved the posterior pole, presumably related to the actively growing melanoma located in the superior nasal fundus. This intraretinal edema was recognized in the macula before exposure to the laser light. The melanoma itself showed complex vascular patterns on fluorescein angiography with extensive leakage of dye that diffused into the overlying retina, where heavy fluorescein staining was seen in the late part of the fluorescein study.

Laser exposure of the macula failed to produce a clinically recognizable reaction in the retina during the treatment, and no changes were recognized on results of a careful clinical examination 5 days after exposure. A fluorescein angiogram 5 days after the laser exposure showed no difference from the fluorescein angiogram obtained immediately before the laser exposure. Although the central visual acuity was reduced to 20/100 immediately after exposure, 5 days after TTT, the central visual acuity had recovered to identify TTT-induced adverse effects in the retina or the pigment epithelium by means of clinical examination or fluorescein angiography. However, we observed histological and ultrastructural abnormalities in the tissue after the eye was enucleated. We believe that these abnormalities can be explained by the presence of the preexisting retinal edema. However, some of the observed abnormalities could have been caused by light alone, as shown by Robertson and Erickson. Although we looked for evidence of vascular closure or coagulative necrosis in the small capillaries in the choroid, we were unable to demonstrate such changes in the choroid in the foveolar region by means of ultrastructural studies.

The absence of recognizable destruction of the retina and retinal vasculature observed in this single experiment does not ensure that vascular closure and retinal destruction will not occur when TTT is used to treat occult choroidal neovascular membrane. However, in this case, with clinical and angiographic evidence of mild retinal edema and no retinal or subretinal blood, a 60-second exposure of 800 mW using a 3-mm beam diameter did not cause clinically recognizable damage to the macular retina, the retinal vessels, or the underlying choriocapillaris and other choroidal vessels.

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Malignant peripheral nerve sheath tumor (MPNST) is an extremely rare orbital tumor and only 34 cases have previously been reported. Only 5 were childhood cases of MPNST occurring in the orbit. We report a sixth case of this disease in the orbit of an 11-year-old girl who had rapidly progressive proptosis and optic nerve compression.

Report of a Case. An 11-year-old girl was referred with a 5-day history of rapidly progressive painless proptosis of the left eye and a corrected visual acuity that had decreased from 6/5 to 6/12 over the previous 24 hours. On examination, the left eye was noted to have a 5-mm axial proptosis with a relative afferent pupillary defect and a swollen optic disc. Ocular motility was unrestricted and she did not complain of diplopia. There was no palpable periorbital mass and no periorbital sensory deficit. She was otherwise healthy with no significant medical history. A magnetic resonance imaging (MRI) scan showed a large, ovoid, intraconal mass in the left orbit that extended from the orbital apex to the posterior aspect of the globe. There was no evidence of extra-orbital extension. The mass was clearly separate from the optic nerve and had produced pressure erosion of the lateral orbital wall. It showed a homogeneous signal on T1 images with small cystic areas on T2 scans. There was diffuse enhancement following contrast, with focal areas of more prominent enhancement (Figure 2).

A medial transconjunctival incisional biopsy of the tumor was performed and 4 pieces of tissue were sent for histologic evaluation. Histologic findings showed a biphasic tumor with a cellular small round blue cell component (Figure 3) merging with a cellular spindle cell component (Figure 4). There was no necrosis, but apoptotic cells were often noted in the specimen. Although mitoses were infrequent (1/20 high-power field), some morphologically abnormal mitotic figures were present. The spindle-shaped cells showed ill-defined cytoplasm and contained hyperchromatic, pleomorphic, serpiginous nuclei. The round cells showed little cytoplasm and contained moderately pleomorphic nuclei with coarse hyperchromatic chromatin and irregular nuclear contours. Nucleoli were inconspicuous. The round cell component contained rosettelike structures with hyperesinophilic fibrillary cores (Figure 5). The overall appearances raised the differential diagnosis of spindle cell neuroblastoma, primitive neuroectodermal tumor (PNET), neuroepithelioma, and MPNST with a PNET-like component. Both the round cell and spindle cell components were positive for S100 protein and glial fibrillary acidic protein (GFAP) (Figure 6). Test results for neuron-specific enolase (NSE) were positive, predominantly in the small round cell component. Test findings for neurofilament, synaptophysin, chromogranin, cytokeratin, CAM 5.2, epithelial membrane antigen, desmin, and actin were all negative. (All antibodies were provided by Dako, Ely, Cambridgeshire, United Kingdom.) Test results for the MIC-2 gene product (Dako) and β2-microglobulin (Dako) were also negative.

Electron microscopy showed that the cells in both the round cell and the spindle cell areas were similar. They contained a few cisternae of rough endoplasmic reticulum and mitochondria. The cytoplasmic matrix contained monoribosomes, polyribosomes, and locally abundant intermediate filaments; in the round cell areas, cells in clusters were closely juxtaposed with no intervening matrix. Where the clusters contacted stroma, cell surfaces exhibited stretches of lamina, as well as bundles of slender collagen fibrils (Figure 7). Better developed lamina was also present over spindle cells (Figure 8). These cells also had long coarse cytoplasmic processes containing relatively large numbers of intermediate filaments and fewer membranous organelles. No glycogen, neuroendocrine granules, processes containing microtu-
bulges, or bundles of striated muscle myofilaments were seen.

The patient underwent left orbital exenteration with a complete apical clearance, and 6 weeks later she received postoperative radiotherapy. She has since made a complete recovery with no recurrence or metastatic disease after 4 years’ follow-up.

**Comment.** Thirty-four cases of MPNST of the orbit have been reported.¹⁻¹⁰ Seventeen arose from the trigeminal nerve, mainly from its suprachiasmal branch. Three previously reported tumors occurred in children. The youngest reported patient, born with Kartagener syndrome, was 4 days old when the tumor was detected on an MRI scan. After confirmation from anterior orbital biopsy results at age 5 days, he underwent an exenteration at age 6 weeks and has been reported to be tumor free at age 27 months.¹ One tumor in the orbit of a 50-day-old male infant showed features of a plexiform MPNST.⁸ Despite orbital exenteration and radiotherapy, he died within 6 months of diagnosis.
The third child had previously received radiotherapy for bilateral retinoblastomas and developed an anaplastic sarcoma arising in an orbital neurofibroma. The fourth child, a 15-month-old boy, underwent lateral orbitotomy with cryoexcision of a retrobulbar MPNST in association with a myxoid neurofibroma. Histologically the MPNST pseudocapsule was intact and 9 years later the child was still disease free. The fifth case was diagnosed in a 23-year-old man who had rapid-onset orbital proptosis and pain in the left eye. Biopsy specimens taken at the time were compared with specimens from an incomplete excision of the tumor taken when he was 5 years old and that was previously diagnosed as fibromatosis. Both specimens were found to be MPNST. He underwent orbital exenteration and was reported to be alive without recurrence 8 months later. This was 18 years after initial tumor presentation and is the longest reported survival.

The current case clearly showed features of a rapidly evolving malignant neoplasm: rapid growth, marked cellularity, mitotic activity, and apoptotic figures, and abnormal mitoses indicated its malignant potential. The ultrastructure indicated schwannian differentiation that supported a diagnosis of MPNST. In addition, the round blue cell component of the tumor showed no immunoreactivity for synaptophysin, MIC-2 gene product, or B2-microglobulin, and electron microscopy showed it was devoid of neuroendocrine granules and processes containing microtubules. All of these features exclude the diagnoses of neuroblastoma, neuroepithelioma, and true PNET.

Meis et al reported a patient with PNET-like foci in 15 cases of nonorbital childhood MPNSTs that closely resemble those in the current case. They found that PNET-like foci do not adversely affect the prognosis. They also determined that 50% of MPNSTs were positive for S100 protein. The presence of GFAP in MPNSTs is uncommon, but Gray et al reported GFAP reactivity in 2 cases in their series.

In conclusion, MPNSTs should be considered in the differential diagnosis of malignant orbital tumors in children. This disease has a poorer prognosis than most childhood malignancies, and complete surgical excision is essential to provide a chance of cure. Our case showed an unusually rapid progression with acute presentation of proptosis and optic nerve compression. Immunohistochemistry showed the presence of GFAP although reports of GFAP positivity are exceptional in MPNSTs. A poorly differentiated PNET-like small cell component was also present.

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Ocular Findings in Spinocerebellar Ataxia 7

Spinocerebellar ataxia (SCA) 7, also known as autosomal dominant cerebellar ataxia (ADCA) type II or olivo-pontocerebellar atrophy with retinal degeneration, is one of at least 14 genetically distinct forms of hereditary SCA. All of these forms are characterized by variable degeneration of the cerebellar cortex, the basal ganglia, the brainstem, the spinal cord, and the peripheral nerves. Prior to the identification of the causative genes, ADCas were divided into 3 subtypes. In ADCA type I, cerebellar ataxia is associated with ophthalmoplegia, optic atrophy, extrapyramidal signs, and dementia. Patients with ADCA type II develop retinal degeneration and cerebellar ataxia. Ophthalmoplegia, extrapyramidal signs, and dementia are variably present. Autosomal dominant cerebellar ataxia type III is described as a “pure” cerebellar syndrome. All 3 ADCA types are genetically heterogeneous. Almost all of ADCA type II cases are due to mutations in the SCA7 locus; thus, SCA7 is unique in that it is the only SCA invariably associated with retinal degeneration. Here, we describe the ocular findings in a patient diagnosed after postmortem examination as having had SCA7.

Report of a Case. A 17-year-old black male died of aspiration pneumonia and a urinary tract infection. No notable developmental or medical problems were evident until the age of 8 years when he was noted to have poor vision. He was diagnosed with retinitis pigmentosa at age 9.5 years and was legally blind (20/300 OD and 20/400 OS) by age 11 years (Figure 1). At age 10 years, he started to have difficulty walking. He had full muscle strength but poor coordination and dysmetric finger-to-nose and knee-chin movements. Speech was slow and dysarthric. There was limited upward gaze, limited adduc-
tion, dysconjugate gaze, and bilateral ptosis. There was no family history of relevant ocular or neurologic diseases.

Electrocardiogram results showed no evidence of cardiac conduction block. Electroencephalogram findings were normal. Magnetic resonance imaging of the head revealed cerebellar atrophy, a dilated fourth ventricle, and thin but otherwise normal-appearing optic nerves. At age 12 years, a muscle biopsy specimen showed no ragged red fibers with the Masson trichrome stain and no abnormal mitochondria by electron microscopy. Electron transport chain (ETC) analysis revealed a partial defect in ETC complex I and normal ETC complexes II, III, and IV. No deletions of mitochondrial DNA were detected by Southern blot analysis; no sequence analysis was performed to search for point mutations in the mitochondrial genome. Nevertheless, the patient carried the diagnosis of an atypical form of mitochondrial disease, such as a variant of Kearns-Sayre syndrome or myoclonic epilepsy and ragged red fiber disease/progressive external ophthalmoplegia.

By age 13 years, the patient was confined to a wheelchair. He began to have myoclonic seizures. A percutaneous gastrostomy tube was placed for feeding. At age 16 years, the patient had respiratory failure requiring assisted ventilation, especially at night. He had 15 hospital admissions in the last year of life for respiratory distress, aspiration pneumonia, and episodes of lethargy and unresponsiveness. One month prior to death, the patient was admitted to the hospital with seizure activity characterized by jerking of the head, both arms, and right leg. A head computed tomography scan revealed no focal lesions. He was treated for presumed status epilepticus, after which an electroencephalogram showed findings suggestive of diffuse cortical dysfunction but no evidence of seizure activity. He developed a left lower lobe pulmonary infiltrate and a urinary tract infection. Given the patient’s poor neurologic and pulmonary status, mechanical respiratory support was discontinued and the patient died the following day.

The right globe and central nervous system were obtained at autopsy. On gross examination, the retinal pigment epithelium (RPE) had a mottled appearance throughout the fundus (Figure 2). Ciliary epithelial cysts containing acellular eosinophilic material were present on microscopic examination (Figure 3) but were not appreciated grossly. The ganglion cell layer of the retina appeared normal. There was diffuse photoreceptor degeneration that appeared more severe in the posterior pole than in the periphery. There were very rare intraretinal pigment deposits and areas with subretinal proteinaceous material. Patches of atrophic RPE were intermixed with hyperpigmented and hypertrophic RPE cells (Figure 4).

Immunohistochemical staining with an antibody against ubiquitin, a component of many types of inclusions, revealed rare intranuclear inclusions (Figure 5). The ubiquitin-positive inclusions were either round and compact or diffuse. We were unable to convincingly detect these inclusions with an antibody against expanded polyglutamine repeats. However, electron microscopy of the retina confirmed the presence of 2 distinct types of intranuclear inclusions (Figure 6). The first type of inclusion was round,
compact, and predominantly filamentous, while the second type was larger and more diffuse with granular and filamentous structures.

The brain weighed 950 g (normal for an adult male is 1350-1450 g). The cerebrum was mildly atrophic and microscopically showed reactive gliosis. There was severe atrophy of the cerebellum with gliosis and only rare Purkinje cells (Figure 7). Severe gliosis and neuronal loss were also found in the brainstem and the spinal cord in a pattern consistent with SCA.

Molecular analysis of the SCA7 gene showed that the patient was a heterozygote, with 1 allele having approximately 12 CAG repeats and the other having 70 to 87 repeats (normal, 6-36 repeats) (Figure 8). DNA from the patient’s parents was not available.

Comment. This case is noteworthy because the diagnosis of SCA7 was made only after postmortem examination. The patient had a prior diagnosis of an atypical mitochondrial disorder because the clinical symptoms overlapped with those found in mitochondrial myopathies and because of an abnormal ETC complex I analysis. The signifi-

Figure 3. Ciliary epithelial cysts contain acellular eosinophilic material (hematoxylin-eosin; original magnification ×40).

Figure 4. Severe photoreceptor degeneration in the posterior pole of the retina (A) with very rare intraretinal pigment deposits (A and B). Patches of atrophic retinal pigment epithelium (RPE) are intermixed with hyperpigmented and hypertrophic RPE cells (A and B) (hematoxylin-eosin; original magnifications ×100 and ×400, respectively).

Figure 5. Retinal intranuclear inclusions containing ubiquitin. Immunohistochemical staining with an antibody against ubiquitin reveals a round, compact, intranuclear inclusion in the inner nuclear layer (A) and a more diffuse, intranuclear inclusion in the ganglion cell layer (B). Intranuclear inclusions are designated by arrows. Immunohistochemistry was performed on formalin-fixed tissue (original magnification ×1000).
cance of the abnormal ETC complex I analysis is uncertain.

Spinocerebellar ataxia 7 was not seriously considered, possibly because of the absence of a positive family history. Like other dominant neurodegenerative disorders, such as Huntington disease, SCA7 shows strong anticipation: the age of onset and disease severity increase with each successive generation. The molecular basis for anticipation in SCA7 is the expansion of a polyglutamine tract in ataxin 7, the protein product of the SCA7 gene. This stretch of glutamine residues is encoded by the repetition of the sequence CAG in the coding region of the gene. The number of CAG repeats (and the encoded polyglutamine tract) varies normally from 7 to 17 repeat units. Rarely and for obscure reasons, an allele with 18 to 35 repeats will arise. Individuals with these intermediate alleles are usually asymptomatic. However, once the repeat has expanded, it is prone to expand even further during parent-to-child transmission and especially during father-to-child transmission. Individuals affected with SCA7

![Figure 6](https://archopht.jamanetwork.com/)

*Figure 6.* An electron micrograph shows 2 intranuclear inclusions in a retinal cell. One is compact and predominantly filamentous (arrow). The second is larger and more diffuse with granular and filamentous structures (surrounded by arrowheads). n indicates the nucleus; c, cytoplasm. Electron microscopy was performed on glutaraldehyde-fixed tissue stained with lead citrate. Scale bar indicates 1 μm.

![Figure 7](https://archopht.jamanetwork.com/)

*Figure 7.* A normal cerebellar cortex (A) compared with the cerebellar cortex in the patient in this report with spinocerebellar ataxia (SCA) 7 (B). There is severe atrophy of the cerebellar cortex in the patient with SCA7, with loss of Purkinje cells (p) and internal granule cells (ig). There are no identifiable Purkinje cells in most sections of the cerebellum; this section is one of the few with a remaining Purkinje cell (seen in the center of the field) (hematoxylin-eosin; original magnification ×40).

![Figure 8](https://archopht.jamanetwork.com/)

*Figure 8.* Molecular genetic analysis of the patient's DNA purified from a fragment of unfixed, frozen liver. The portion of the SCA7 gene containing the polyglutamine region was amplified by polymerase chain reaction (PCR). The PCR-amplified DNA products were separated by denaturing gel electrophoresis. Size was determined by comparing the migration of the PCR-amplified DNA products with a DNA sequence ladder of known size (not shown). DNA from a patient known to have spinocerebellar ataxia (SCA) 7 is the positive control (+). DNA from an unaffected individual is the negative control (−). DNA from our patient is in the middle lane (pt). One allele of the SCA7 gene in our patient contains expanded CAG repeats (70–87 repeats). The second allele is wild type with approximately 12 repeats. Multiple bands are due to “stuttering” of the polymerase as it replicates the polyglutamine region. Numbers along the right side of the gel indicate the number of CAG repeats.
carry an allele with 37 to 200 repeat units. Thus, one possible explanation for why this patient did not have a positive family history is that one parent was an asymptomatic carrier of an intermediate allele, and the pathologic expansion of the repeat occurred between generations.

Retinal degeneration is always present in patients with SCA7. The onset of visual symptoms may precede or follow the onset of neurologic symptoms. The disease affects cone function more severely than rod function. Patients never complain of night blindness. The first visual complaint is usually reduced central visual acuity or abnormal color vision.1,2 Electoretinograms document that cone function is more severely impaired than rod function. Fundus examination early in the disease shows atrophy of the RPE in the macula; later there is attenuation of retinal vessels and a mottled RPE throughout the fundus. There is little or no intraretinal pigmentation of the sort that is ordinarily seen in retinitis pigmentosa.

Most but not all patients with ADCA type II harbor mutations in the SCA7 gene. Giunti et al8 identified one family with ADCA type II that did not have CAG expansion in the SCA7 gene and no linkage to the SCA7 locus, indicating genetic heterogeneity. Furthermore, Babovic-Vuksanovic et al9 reported a case of SCA with retinal degeneration in an infant who died with a severe form of SCA2. These rare cases emphasize the importance of molecular genetic analysis to establish the diagnosis. The ocular pathologic characteristics of 2 cases of ADCA type II described by To et al8 and Martin et al10 are now known to be from families with SCA7 gene defects determined by DNA analysis (Eliot Berson, MD, oral communication, 1999, and Mauger et al,10 respectively).

Neuronal intranuclear inclusions are a common feature of diseases related to polyglutamine expansion. In Huntington disease, SCA1, and SCA3, intranuclear inclusions develop mainly in neurons from regions affected by the disease,11-13 leading to the hypothesis that the formation of intranuclear inclusions is an important step in the neurodegenerative process. However, in SCA7, intranuclear inclusions are not restricted to regions affected by the disease.14 These findings suggest that the inclusions may be necessary but not sufficient to cause cell dysfunction and death.

In this study, we described the ultrastructural appearance of 2 types of intranuclear inclusions in the retina of a patient with SCA7. The diffuse, granulofilamentous inclusions resemble the inclusions found in the retina of one patient with early-onset SCA7 described by Mauger et al.10 Similar granulofilamentous inclusions have been found in patients with Huntington disease and in mice hemizygous for a mutant form of human huntingtin (hd).11,15 The compact, filamentous inclusions in our SCA7 case differ from those described by Mauger et al10 and most closely resemble the amyloid-like structures observed in mice homozygous for the hd mutation.15 As in the SCA7 case reported by Mauger et al, the retinal intranuclear inclusions in our patient contained ubiquitin and were present in the inner and outer nuclear layers as well as the ganglion cell layer. Our data support the finding of Mauger and coworkers10 that intranuclear inclusions in the retina are not restricted to the neuronal population that degenerates.

To our knowledge, no previous report of the ocular pathology of presumed SCA7 disease mentions cilary epithelial cysts. Such cysts containing proteinaceous material, as found in our case, are considered a specific feature of multiple myeloma and other hypergammaglobulinemic conditions,16 which were not present in this case.

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15. Johnson BL, Storey JD. Proteinaceous cysts of the retinal pigmentation of the sort that is ordinarily seen in retinitis pigmentosa.

Acquired Retinal Myelinization in Neurofibromatosis 1

Myelination of the anterior visual pathways begins centrally at the lateral geniculate body and is com-
completed at term. This process normally terminates at the lamina cribrosa, but it occasionally may extend into and beyond the peripapillary retinal nerve fiber layer. Congenital retinal myelination is not uncommon, occurring in 0.3% to 0.6% of the population as an isolated developmental anomaly, or rarely as part of a generalized disorder, such as the Goltz-Gorlin syndrome, or the syndrome of anisometropia high myopia, and amblyopia.1 Although recent evidence suggests that the retinal myelination may progress in such cases,2 acquired retinal myelination is exceptionally rare.3 We describe 2 cases in which myelinated retinal nerve fibers appeared in children with neurofibromatosis 1 (NF1) and optic nerve glioma. In both cases, spontaneous improvement in visual function preceded the retinal myelination.

**Report of Cases.** Case 1. An 8-year-old boy was referred to us with reduced vision and optic disc swelling in the right eye. There was a maternal family history of NF1, and he had cutaneous features of NF1 and Lisch nodules. The right eye was proptosed, with optic disc edema, opticociliary shunt vessels, and a relative afferent pupil defect (RAPD) (Figure 1). Corrected visual acuity was reduced to 20/80 OD, and a magnetic resonance imaging (MRI) scan confirmed the presence of an optic nerve glioma. Visual field testing, which was reliably repeatable in this child, showed an enlarged blind spot and peripheral constriction on the right side. No treatment was initiated, and annual follow-up was arranged.

Within a year, visual acuity 20/30 OD, the RAPD resolved, and the visual field enlarged. The disc edema resolved, and the shunt vessels disappeared.

Four years after the initial visit, examination showed myelinated nerve fibers adjacent to the right optic disc (Figure 2). Visual acuity was stable at 20/30 OD, and the MRI findings were unchanged. The retinal features have remained unchanged for 4 years.

Case 2. An 8-year-old boy was referred with reduced vision and a pale left optic disc. He had features of segmental NF1, with café-au-lait spots on the left chest wall and the imaging features of a left optic nerve glioma extending to the optic nerve head on MRI scan (Figure 3). Corrected visual acuities were 20/15 OD and 20/30 OS with left optic atrophy. A full systemic evaluation was performed, but no treatment was initiated. Visual acuity remained stable during the next 2 years, and then gradually improved to 20/20 OS. Five years after the initial visit, he had developed segmental myelination of the peripapillary retinal nerve fibers in the left eye (Figure 4). These findings have remained unchanged for 2 years.

**Comment.** Myelin is deposited in the central nervous system by oligodendrocytes at the time of birth, completing myelination of the central white matter by 12 months of age. While the retinal myelination of the optic nerve head may appear similar to the myelination of the central nervous system, the biology of myelination is different. Myelination of the optic nerve head most likely occurs through a process of axonal sprouting and oligodendrocyte migration. The myelination process is dependent on a coordinated interaction of the axon, oligodendrocyte, and glial cells. There is no evidence that myelination occurs in the peripheral nervous system, and the mechanism of myelination in the central nervous system is not well understood. The myelination process occurs in the developing brain and spinal cord, where myelination is essential for the proper functioning of the nervous system. Myelination is a complex process that requires precise coordination of cellular function. The myelination process involves the orchestrated activities of multiple cell types, including glia, neuronal precursors, and other cell types. The myelination process is critical for the proper functioning of the nervous system, enabling efficient and rapid transmission of neural signals.
drocytes. The 2 major glial cells of the central nervous system (the type 2 astrocyte and the oligodendrocyte) are derived from stem cells known as oligodendrocyte precursor cells, which actively produce myelin prenatally. Myelination ceases at birth as the oligodendrocytes mature into adult type cells and the biochemical stimulus for myelination (notably platelet-derived growth factor) is withdrawn.4

The mechanisms of termination of the myelination at the lamina cribrosa are not clearly understood. This process is important, as opaque nerve fibers would affect vision. Regulatory proteoglycans have been shown to determine where the retinal ganglion cell body ends and the axon begins. This ganglion-axon junction is at the level of the lamina cribrosa in the human optic nerve. Myelination is limited to the axon, and therefore does not extend beyond the lamina cribrosa.5

Certain animals such as rabbits lack a lamina cribrosa, and myelinated retinal nerve fibers are a normal feature of their eyes. The lamina cribrosa may therefore act as a physical barrier to keep oligodendrocytes out of the retina.

There is experimental evidence of a physical barrier at the ocular end of the rat optic nerve, and a similar mechanism has been postulated in humans.6 Myelination could occur postnatally if the barrier were disrupted and/or the oligodendrocytes were stimulated. The barrier may be directly distorted by the tumor as in case 2, or disrupted by disc edema in case 1. Previously described cases of acquired retinal myelination have occurred following resolution of papilloedema7 or associated with optic disc drusen8, where there would be disruption of the lamina cribrosa.

Stem cell proliferation in NFI occurs due to local inactivation of a tumor suppressor gene.7 In the anterior visual pathway, this process produces optic glioma—characteristically an indolent tumor. It is recognized that visual function in optic gliomas can improve spontaneously, with improvement in the scan appearance.8 The improvement in vision in this case was most likely not due to tumor regression, but to axonal remyelination by oligodendrocytes locally reactivated by the same process that triggered the optic glioma. If the lamina cribrosa is also disrupted, remyelination could extend into the retina, with the process stopping, as the stem cell proliferation is self-limiting.4

These 2 cases, therefore, provide an insight into the complex dynamic of focal tissue growth disorders in NF1. Tumor growth is not exponential, but modified by focal repair mechanisms.

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Bilateral Giant Macular Holes With Excellent Visual Function

Eyes with large macular holes have poor visual acuity and poor visual function in general. A previous report9 indicated that visual acuity of better than 20/50 was observed in only 1% of eyes that had a macular hole larger than 400 µm with no posterior vitreous detachment. We report a case with large bilateral macular holes, 1800 µm in vertical diameter in the right eye and 1500 µm in the left eye. The visual acuity was surprisingly good, ie, 20/40 OU, and the stereoview was 50 seconds with the Titmus stereo test. The possible reason for this good visual outcome is discussed.

Report of a Case. A 33-year-old woman was referred to our department with bilateral macular holes. She had first noticed a small scotoma about 2 years previously and experienced a gradual decrease in visual acuity. She had no personal or family history of ocular disease and did not use any medications.

Her best-corrected visual acuity at the time of her first visit was 20/40 OD (−5 diopters [D] sphere) and 20/40 OS (−5.0 D sphere). Her best stereoview was 50 seconds according to the Titmus stereo test. Fundus examination showed a large macular hole in each eye with vertical diameters of 1800 µm OD and 1500 µm OS (Figure 1). The retina partially bridged the hole in her right eye. No posterior vitreous detachment was observed in either eye. Fluorescein angiography showed a window defect corresponding to the hole. Microperimetry images obtained by scanning laser ophthalmoscopy showed that the fixation points were at the upper edges of the macular holes in both eyes (Figure 2). Optical coherence tomography demonstrated a detailed structure around the holes, the edges of which were swollen inferiorly in the right eye (Figure 3A) and inferiorly and superiority in the left eye (Figure 3B). Both eyes retained similar visual function during a 7-month observation period.

Comment. Eyes with stage 3 macular holes tend to have progressive deterioration of visual acuity before the vision stabilizes at 20/200 or worse.9 A previous report indicated that visual acuity better than 20/50 is observed in only 1% of eyes that had a macular hole larger than 400 µm with no posterior vitreous detachment.9


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Figure 1. Color fundus photographs. A. The macular hole in the right eye is 1800 µm in vertical diameter and the retina partially bridges the hole. B. The hole in the left eye is 1500 µm in vertical diameter.

Figure 2. Microperimetry images obtained by scanning laser ophthalmoscopy. The crosses represent fixation points in the right (A) and the left (B) eyes. The fixation points are at the upper edges of the macular holes for eccentric fixation. The open squares indicate a dense scotoma at that part of the hole; the white squares indicate the points at which the stimulus was recognized.
Our patient had surprisingly good visual acuity compared with that of patients with smaller holes. Moreover, bilateral fixation points were at almost the same locus in each eye, so that each eye could have steady fixation with that locus.

Although the cause of our patient’s excellent visual function including visual acuity and stereopsis was uncertain, we assumed that the macular hole function was related to the fixation loci and stability. We theorize that the bilateral enlargement of the holes and the shifting of the fixation points occurred simultaneously and gradually in our patient. Because of this, we believe, our patient retained good visual function.

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meningiomas. Immediate imaging was not recommended since these masses are slow growing. Subsequently, other intracavernous mass lesions (aneurysms) were found to produce the syndrome.

However, unruptured, extracavernous, intradural aneurysms may rarely cause primary aberrant regeneration. Our patient is the fourth in the literature, to our knowledge, in whom a PCOM aneurysm has caused primary aberrant regeneration. In 1952, Levin described a 68-year-old woman with primary aberrant regeneration who subsequently died of a ruptured aneurysm at the junction of the left internal carotid and PCOM arteries. Cox et al. described a 76-year-old woman with primary aberrant oculomotor regeneration and chronic eye pain due to a large, partially thrombosed aneurysm at the junction of the right PCOM and internal carotid arteries. No surgery was performed. Varma and Miller described a 64-year-old woman with painless primary oculomotor nerve regeneration caused by an aneurysm at the junction of the right PCOM and internal carotid arteries. Their patient underwent successful aneurysm clipping.

Our patient had painless primary aberrant regeneration caused by a partially thrombosed aneurysm at the junction of the left PCOM and posterior cerebral arteries. This is the first reported instance of an aneurysm at this location causing primary oculomotor nerve synkinesis. Although primary aberrant regeneration is most likely associated with slow-growing cavernous sinus le-

Figure 1. In primary position (center), there is a left hypotropia and left exotropia. A mild right ptosis is present. There is limited elevation, adduction, and infraduction in the left eye. Upper eyelid retraction is seen on adduction and infraduction in the left eye (lower left).

Figure 2. Axial T1-weighted pregadolinium (A) and gadolinium-enhanced (B) magnetic resonance image showing a 1-cm enhancing mass in the interpeduncular cistern region (arrows), consistent with a partially thrombosed aneurysm.

Figure 3. Frontal view of the cerebral angiogram of the posterior circulation following injection of the right vertebral artery. A focal outpouching is seen (arrow) at the P1-P2 junction of the left posterior cerebral and posterior communicating arteries, consistent with a partially thrombosed aneurysm.
sions, PCOM aneurysms rarely cause this syndrome. We believe that patients with primary aberrant oculomotor nerve regeneration should undergo immediate imaging to detect potentially treatable extracavernous, intradural aneurysms.

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Unilateral Mydriasis Associated With Exposure to Flea Spray

Anisocoria is a frequently encountered condition that often requires neurologic evaluation. Although it may occur with third nerve palsy, other causes include benign conditions, such as pharmacologic dilation, local iris sphincter abnormalities, tonic pupil, or sympathetic irritation.1 Unilateral miosis has been reported to result from exposure to cholinesterase inhibitors found in both flea foggers2 and pet flea and tick collars3. We report a case of unilateral mydriasis associated with exposure to flea spray.

Report of a Case. A 3½-year-old boy was brought to the emergency department by his parents, who noticed that his pupils were of unequal size. There was no history of trauma, recent illness, medication use, or access to ophthalmic drops. Further inquiry revealed that the child had been playing with the family dog, which was recently treated with Sergeant’s Flea and Tick Spray (Sergeant’s Pet Care Products, Omaha, Neb). His behavior and activity had been normal. Vital signs were normal for his age, and results of a pediatrician’s examination revealed no abnormalities other than anisocoria. Ophthalmologic examination results revealed a visual acuity of 20/30 OU using Allen figures at near. Anterior segments were normal when examined with a handheld light. Versions, alignment, and dilated fundus examination results were normal. There was no evidence of disc edema. Intraocular pressure readings were 13 mm Hg OD and 14 mm Hg OS. Under lighted conditions, the right pupil was 6.5 mm and the left pupil was 4 mm. In dim light, the right pupil measured 7 mm and the left pupil measured 5 mm. Both the direct and consensual pupillary light responses were 1+ OD and 3+ OS. The near response was also 3+ OS and 1+ OD. Results of computed tomography of the head performed without contrast showed no evidence of intracranial masses, edema, or dilated ventricles. The mydriasis and pupillary reactivity of the right eye had improved by the examination on the following day. Although the child failed to return for a subsequent examination, a telephone conversation with his mother revealed that the pupil inequality had resolved and that he was doing fine.

Comment. The active pesticide in Sergeant’s Flea and Tick Spray and related products permethrin is a type I pyrethroid. Pyrethroids have been found to produce potent sympathetic activation; local effects, such as paresthesia, have been reported with skin contamination.4 Additionally, α-adrenergic-mediated effects have been noted in animal studies using allethrin, another type I pyrethroid.5 We suggest that the patient’s unilateral mydriasis may have been due to a local effect of permethrin that occurred after inadvertent rubbing of the eye following skin contamination. The local sympathetic effect did not alter near vision but produced mydriasis that was partially overcome by bright light and significantly improved the following day. To our knowledge, this is the first reported case of mydriasis occurring in association with exposure to flea pesticide products. It is important to consider exposure to pesticides during the evaluation of anisocoria since it may prevent costly and unnecessary imaging in the otherwise healthy patient.

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Acute Psychosis Following the Use of Topical Ciprofloxacin

Ciprofloxacin hydrochloride is a fluoroquinolone antimicrobial frequently used in both ophthalmic and general medical practice. Whereas adverse effects of this drug are not uncommon following its systemic use, they are uncommon following its topical use. We present the case of a young woman who developed an acute psychotic reaction following the use of ciprofloxacin eyedrops. To our knowledge, this is the first reported case of such a complication following topical ciprofloxacin use.
Report of a Case. An otherwise fit and healthy 27-year-old woman came to the emergency eye clinic with a 3-day history of bilateral reddened eyes associated with ecchymosis and swelling of the eyelids. There was no history of pain or impairment of vision. Examination results revealed severe bilateral conjunctival congestion, marked papillary reaction, and membranous conjunctivitis. The results of the remainder of the ocular examination were entirely normal and there was no lymphadenopathy. The patient had no history of any systemic complaints, was taking no medication for therapeutic or recreational use, did not have alcoholism, and did not smoke. Conjunctival swabs were taken and sent for microbial isolation and sensitivity analysis and the patient was prescribed ciprofloxacin eye drops, 1 drop hourly, in each eye. About a half hour after the third dose, the patient complained of dizziness and light-headedness. Following this, family members noted a distinct change in the behavior of the patient, who began to have well-defined visual hallucinations, ill-defined auditory hallucinations, and irrational conversation. The next day, the patient was seen in the emergency eye department, accompanied by her mother, with increasing behavioral problems. A psychiatric opinion was sought. The patient was deemed to have had an acute psychotic reaction secondary to topical ciprofloxacin. The patient was advised to stop using ciprofloxacin eye drops (nearly 24 hours after initiation of treatment) and began taking teicoplanin (1%) eye drops. Within about 12 hours of changing the treatment, the patient and family members noted an improvement in behavior and within a further 12 to 14 hours, the hallucinations and behavioral disturbances disappeared completely. The patient was later able to describe her visual and auditory hallucinations in detail. The conjunctivitis responded completely to the teicoplanin regimen.

Comment. Ciprofloxacin is a fluoroquinolone antimicrobial that inhibits DNA gyrase, and when given orally, exhibits 70% bioavailability and attains peak serum levels ranging between 1.5 and 2.9 µg/mL after a single 500-mg dose, with 19% of an oral dose being excreted as metabolites in both urine and feces. In addition to cutaneous and gastrointestinal adverse effects, central nervous system adverse effects, such as dizziness and lightheadedness, acute psychosis, and other neuropsychiatric disorders have been described following its systemic use. In extremely rare situations, more serious central nervous system effects, such as seizures, have also been described. Cases of ciprofloxacin-induced psychosis have been reported, with resolution of psychotic symptoms on discontinuation of the drug and reappearance of these symptoms on resumption of ciprofloxacin treatment. However, to our knowledge, there is no report of these adverse effects following the use of topical ciprofloxacin eye drops. In the case reported here, we believe that the systemic adverse event experienced by this patient was an idiosyncratic one, aided by the increased systemic absorption of the drug secondary to severe conjunctival inflammation. Although the patient did not resume use of the topical ciprofloxacin, the absence of other confounding illnesses (drug or alcohol abuse and previous psychiatric disturbances) and the rapid resolution of psychosis support the case for topical ciprofloxacin as the causative factor. Whereas psychotic reactions are well known after the use of atropine and cyclopentolate eye drops, this is the first reported case, to our knowledge, of such a reaction after the use of ciprofloxacin eye drops. Therefore, the possibility of such an adverse effect should always be kept in mind in patients using these drops, particularly in young women, who seem to be especially sensitive to these effects.

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Here’s Egg in Your Eye: An Unusual Penetrating Eye Injury

Many unique, interesting, and even bizarre cases of penetrating eye injuries have previously been reported. Examples include injuries caused by a fishing hook and a golf tee, pecking injuries due to magpies and coromorants, and even a boa constrictor bite that perforated its owner’s right eye. This report presents a case of a penetrating eye injury caused by an exploding emu egg, which to the best of our knowledge is the first such case reported in the ophthalmic literature. (Note: The emu is a large native bird of Australia, and adult birds may grow to more than 6 ft in standing height. Emu eggs are routinely about 5 times the size of a normal chicken egg.)

Report of a Case. A 10-year-old boy sustained a severe penetrating injury to his left eye from an exploding emu egg. He was expelling the egg’s contents with an air compressor when yolk blocked the exit hole, causing the egg to explode. An examination revealed a full-thickness paracentral laceration of the cornea, extending from the superior to inferior limbus. The boy’s visual acuity was light perception only OS. A computed tomographic scan revealed a large foreign body lodged in the nasal retina.
Later that day, the boy underwent surgery. The prolapsed vitreous was excised, and the corneal wound was sutured so that the intraocular pressure could be maintained. A 3-port pars plana vitrectomy and lensectomy were performed. The eggshell fragment embedded in the nasal retina was identified and removed from the eye with intraocular forceps via the corneal laceration, which was reopened (Figures 1 and 2). The corneal wound was resutured, an inferonasal segmental scleral buckle was applied, and perfluoropropane gas was injected into the eye.

An intraoperative vitreous biopsy was obtained, and intravitreal injections of vancomycin hydrochloride (1 mg/0.1 mL) and ceftazidime (2.25 mg/0.1 mL) were administered. Biopsy cultures revealed a mixed growth of viridans streptococci, Haemophilus parainfluenzae, Neisseria species, and Staphylococcus aureus (coagulase-positive). Oral and topical ciprofloxacin hydrochloride therapy was commenced postoperatively.

Six months later, further surgery was performed involving a sutured-in posterior chamber intraocular lens. At the most recent follow-up visit, the boy’s pinhole visual acuity had improved to 20/30 OS.

**Comment.** For penetrating eye injuries involving organic matter, it is essential to collect vitreous and/or other appropriate intraocular specimens during the initial surgical procedure. Once intravitreal antibiotics are given, it may be very difficult to isolate the infecting organisms from subsequent aspirates. This is particularly important in penetrating injuries with a high risk of infection such as those including animal, soil, or water contamination. In addition, when gas or oil exchange is performed, injecting intravitreal antibiotics beforehand enables an appropriate concentration to be maintained after the exchange.

This case report presents a very unusual penetrating eye injury that, with appropriate and timely treatment, resulted in a good clinical outcome.

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Figure 1. Removal of the emu eggshell fragment from the eye via the corneal laceration.

Figure 2. The colorful, triangular, 11-mm emu eggshell fragment adjacent to the corneal laceration.