Conjunctival Papillomas
Caused by Human Papillomavirus Type 33

Conjunctival papillomas are associated with human papillomavirus (HPV) infection. In children, the lesions are typically manifestations of an infection acquired during delivery. In adults, conjunctival papillomas are most likely venereal and are often associated with anogenital lesions. Papillomas due to HPV more frequently progress to malignancy in patients with the human immunodeficiency virus (HIV) infection. Human papillomavirus types 6, 11, 16, and 18 have been identified in benign and malignant conjunctival lesions using various antigen and DNA detection techniques. For the first time, to our knowledge, we report the finding of HPV type 33 in conjunctival papillomas excised from an HIV-positive patient.

Report of a Case. A 34-year-old HIV-positive man complained of bilateral conjunctival lesions of 4 years' duration. Ten years earlier, he was diagnosed as having HIV after developing pneumocystis pneumonia, a Mycobacterium avium-intracellulare infection, and perianal HPV condylomata acuminata. While receiving highly active antiretroviral therapy (HAART), including indinavir sulfate, nevirapine, and combivir, he has had no new opportunistic infections and his CD4+ cell count has increased above 200/mm³. He sought ophthalmic care because of occasional bleeding from the conjunctival lesions. An initial ophthalmic examination revealed bilateral inferior palpebral conjunctival papillomas that were excised from the right eye. The results of a histopathologic examination showed conjunctival papillomas without atypia. The results of an immunohistochemistry test for HPV types 6, 11, 16, 18, 31, and 33 was negative. The conjunctival lesions recurred, and he was referred to the National Eye Institute, Bethesda, Md. The results of our examination were unremarkable, except for the presence of 1.2- to 1.5-mm nodular lesions on the right upper and lower palpebral conjunctiva and large, confluent, verrucous lesions involving the left upper and lower palpebral conjunctiva (Figure 1). A left palpebral conjunctival excisional biopsy was performed. A histopathologic examination of the biopsy specimen revealed papillary fronds of acanthotic squamous epithelium without atypia and koilocytic changes overlying inflamed fibrovascular cores (Figure 2). Nucleated keratinocytes from the paraffin-embedded specimen were microdissected under direct visualization. After proteinase K digestion, DNA sequences for HPV genotypes 16, 18, and 33 were amplified with a kit (PCR Human Papillomavirus Detection Kit; Pan Vera, Madison, Wis) and transblotted for Southern blot hybridization. Briefly, the common sense primer for HPV types 16, 18, and 33 was 5'-AAGGGCGTAACCGAAATCGGT-3' and the antisense primers of each HPV strain were as follows: 5'-GTTTGAGCTCTTGTCATA-3' for HPV 16, 5'-GTGTTCTGGTCCGTCACA-3' for HPV 18, and 5'-GTCTCCATGGTTCGGACA-3' for HPV 33. The hybridization probes were 5'-CATTTTATGCACCAAAAGAGAACATGACTGACTA-3' for HPV 16, 5'-TGGAGAACACACCAAAATATGTCGCA-3' for HPV 18, and 5'-CATTTCAGGCTAGACTGACTATG-3' for HPV 33. The polymerase chain reaction was performed for each HPV strain under the following conditions: 94° for 30 seconds to denature the primers, 55° for 2 minutes for primer annealing, and 72° for 2 minutes for primer extension. The reaction was repeated for 35 cycles, con-
cluding with a final extension at 72°C for 10 minutes. The results demonstrated HPV type 33 DNA sequences in the epithelium of the conjunctival papillomas (Figure 3). Postoperatively, the patient was unavailable for follow-up.

Comment. Human papillomavirus is an oncogenic double-stranded DNA papovavirus that infects keratinocytes and causes benign and malignant hyperproliferative squamous epithelial tumors. With approximately 100 subtypes identified, HPV is now the most common sexually transmitted disease. Human papillomavirus is the cause of verrucae (skin warts), condylomata acuminata (vulvar or genital warts), and mucocutaneous papillomas, which represent 7% to 12% of all conjunctival lesions.1,4 Most commonly associated with benign anogenital lesions and respiratory papillomas, HPV types 6 and 11 are classified as low-risk subtypes because they rarely progress to invasive cancer. Human papillomavirus types 16 and 18 are considered high risk because they are associated with epithelial dysplasia and squamous cell carcinomas, particularly in the uterine cervix and anal canal. Human papillomavirus types 31, 33, 35, 45, 51, 52, and 56 have an intermediate risk of malignancy.3

 Conjunctival HPV infection may be established during delivery through an infected birth canal, by sexual contact, or by autoinoculation. Human papillomavirus antigens are reported in 5% to 45% of conjunctival papillomas, with HPV types 6 and 11 most commonly found in papillomas from children and HPV types 16 and 18 more frequently associated with dysplasia and carcinoma in older patients. Normal conjunctiva has also been shown to harbor HPV antigens.2,6

 Human papillomavirus type 33 is an uncommon genotype found in benign, dysplastic, and malignant lesions. In a study2 defining the distribution of HPV genotypes in male genital lesions, it was detected in only 1 (0.6%) of 175 specimens. Seropositivity to HPV type 33 increased with age in a study6 of eastern European women. Primarily found in anogenital lesions, recently HPV type 33 has been associated with breast cancer in Chinese and Japanese patients.9

 Infection with HIV increases the risk for HPV-associated malignancy and may be a cofactor linking HPV infection and neoplasia.2 The immunodeficiency secondary to HIV may facilitate the oncogenic effects of HPV by altering the host susceptibility to HPV infection and impairing immune tumor surveillance. A direct molecular interaction between HIV and HPV could also promote the development of cancer. Recently, it has been shown that the HIV-1 tat protein potentiates the expression of HPV oncoproteins.3

 The effect of HAART in HIV-infected patients with HPV disease is unclear. Heard and coworkers10 attributed the reduced prevalence of cervical HPV lesions in HIV-positive women treated with HAART to their increased CD4+ cell count. Similarly, anal HPV lesions were more likely to regress in HIV-positive men with higher CD4+ cell counts who were receiving HAART. Other studies3 involving HIV-positive men with anal HPV lesions who were receiving HAART, however, suggest that anal HPV does not regress and that the improved survival from HAART may paradoxically cause an increased risk of anal cancer.

 An increased incidence of conjunctival malignancy in Africa has been attributed to the combination of HIV-induced immunosuppression, HPV infection, and UV light exposure.3 This finding supports the combined effect of HIV and HPV infections on the risk of ocular neoplasia. We report for the first time, to our knowledge, the presence of HPV type 33 in conjunctival papillomas. Although the conjunctival papillomas in our patient were benign, we suspect that the coincidence of the HIV infection and the oncogenic HPV type 33 places the patient at an increased risk for recurrent and persistent conjunctival papillomas and a conjunctival malignancy. Further follow-up is needed to determine if HAART will ameliorate or potentiate the patient’s risk of ocular disease.

Ronald R. Buggage, MD
Janine A. Smith, MD
Defen Shen, PhD
Chi-Chao Chan, MD
Bethesda, Md

Corresponding author and reprints: Dr Buggage, National Eye Institute, National Institutes of Health, 10 Center Dr, Bldg 10, Room 10N112, Bethesda, MD 20892-1857 (e-mail: BuggageR@intra.nic.nih.gov).

Bilateral Iridociliary T-Cell Lymphoma

Intraocular lymphoma is generally of the B-cell type, commonly affecting the posterior segment of the eye, and in most cases is associated with central nervous system (CNS) lymphoma. Primary involvement of the anterior uvea is very rare. T-cell lymphoma is not commonly seen in the eye. We describe a patient with non-Hodgkin lymphoma (NHL) of the T-cell type affecting primarily the iris and ciliary body of both eyes as the first manifestation of the systemic disease.

Report of a Case. A 31-year-old man came to our clinic with left anterior uveitis of 4 weeks’ duration that was unresponsive to topical steroids. During the previous weeks, he had noticed a progressive worsening of his vision with mild ocular discomfort in his left eye. No pain or redness was present. His history was remarkable for oral drug abuse (3,4-methylenedioxyamphetamine [Ecstasy]) and lysergic acid diethylamide. He denied intravenous drug use and the posterior pole was unremarkable (B-scan, 10 MHz). An anterior chamber tap from the left eye revealed a ciliary body mass. Marked engorgement of the iris vessels was present. The pupil was severely distorted (pulled upward) and mid-dilated. The lens was clear. No cells were present in the vitreous, and the posterior segment was normal in both eyes.

The combination of iris distortion and infiltration with painless severe intraocular inflammation raised the possibility of a tumor masquerading as anterior uveitis. Investigations included an ultrasound examination (high resolution, 20 MHz) of the eyes that revealed a ciliary body mass pushing the iris forward. This occurred in both eyes but was more pronounced in the left eye (Figure 3 and Figure 4). Bilaterally, the anterior choroid was thickened, whereas the posterior pole was unremarkable (B-scan, 10 MHz). An anterior chamber tap from the left eye was performed twice, but microbiologic and cytolologic evaluations were noncontributory. Findings from the uveitis workup, including a complete blood cell count, erythrocyte sedimentation rate, antinuclear antibody test, VDRL test, purified protein derivative (tuberculin) test, human immunodeficiency virus test, and chest x-ray films, were within normal limits. Because of complaints of paresthesia in both legs, the patient underwent a neurologic examination, computed tomography of the brain, and lumbar puncture, which all yielded normal results.

Within a few days, the ocular disease progressed rapidly in both eyes. Iris and anterior chamber angle infiltration increased, leading to an
increased intraocular pressure of 28 mm Hg OS. In view of the lack of response to topical steroids, a diagnostic biopsy of the left eye was performed. During the procedure, the iris was noted to be massively infiltrated and extremely fragile. Behind the iris, a white plaque of cells was seen on the lens surface with localized lens opacity behind it.

A few iris pieces were excised, fixed in formalin, and embedded in paraffin. All fluid washed from the anterior chamber during the procedure was collected and underwent a cytologic evaluation. The biopsy specimen from the nodule in the iris was composed of diffuse sheets of large atypical lymphoid cells (Figure 5). Apoptotic bodies and mitotic figures were seen. The specimen underwent immunohistochemical staining, the atypical cells stained with leukocyte common antigen and CD3 (pan-T-cell marker) (Figure 6) but did not stain with CD20, CD79-α, CD30, terminal deoxynucleotidyl transferase, myeloperoxidase, neuron-specific antigen, or HMB-45. The morphologic appearance together with the immunophenotype of the tumor were diagnostic for peripheral large T-cell lymphoma. An additional systemic workup, including a bone marrow examination, total body computed tomography, and brain magnetic resonance imaging, disclosed no systemic involvement.

The patient was treated with systemic chemotherapy consisting of cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone. Signs of uveitis regressed rapidly in both eyes with melting of the iris mass lesion. However, a recurrence was noted in the left eye 2 weeks later. A new well-defined iris mass was seen in addition to a recurrence of the pseudohypopyon and increased intraocular pressure (Figure 7). A newly appearing dense vitreous infiltration was noted. Central nervous system involvement was ruled out with brain magnetic resonance imaging.

A more aggressive second course of chemotherapy was started following the Magrath protocol. A high dose of intravenous methotrexate and leucovorin calcium was added. Methotrexate was administered intrathecally as well as intravitreally (400 µg/0.1 mL injected twice weekly, 7 times). The second course of chemotherapy induced a rapid response. The white lesion resorbed completely, and the patient remained stable during 9 months of follow-up (Figure 8). The vitreous became free of cells after 7 injections of intravitreal methotrexate. The ciliary body mass and choroidal infiltration had totally disappeared at a repeated echographic examination 4 months after the onset of disease. Visual acuity im-

Figure 5. Sheets of atypical large lymphoid cells are seen (hematoxylin-eosin stain, original magnification × 40).

Figure 6. The atypical lymphoid cells stain positively with the immunohistochemical stain CD3 (pan-T-cell marker, original magnification × 40).

Figure 7. Left eye appearance after the first course of treatment with cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone. After an initial good response, regrowth of the iris lesion was noticed.
proved to 20/20 OD and 20/40 OS and remained stable. Eight months after the diagnosis of ocular lymphoma, skin lesions were noticed and lymphomatous cells were found in the biopsy specimen.

Comment. We present an unusual manifestation of bilateral iridociliary T-cell lymphoma masquerading as steroid-resistant uveitis in an otherwise healthy young patient. Similar iris lymphoma cases have been described in 6 patients, all of whom showed systemic involvement of the disease.1-3,7,9 In 3 of these patients, primary iris infiltration was noticed clinically3,7,8; these patients were affected by systemic NHL (bone marrow and lymph node–visceral lymphoma). The other 3 reported cases exhibited a late iris involvement, with a delay of more than a year between the initial appearance of nonspecific uveitis and the subsequent clinical iris infiltration. In these cases, the lymphoma involved the CNS as well as the eye.1,2,9

The Table summarizes the clinical findings of the 6 cases of intraocular NHL with clinical iris involvement previously reported in the literature, in comparison with our case. Velez et al2 reported 2 cases of large B-cell lymphoma, but only one of them had clinical iris infiltration and appears in our table. One of the reported cases was described as B-cell lymphoma, 2 of them were referred to as reticulum cell sarcoma with no specification of cell type, and 3 were considered T-cell lymphoma. All of the patients with T-cell lymphoma, including ours, had systemic lymphomatous involvement (with only 1 case of additional infiltration of the CNS), and all but one showed an early anterior segment involvement.1

Intraocular lymphoma may involve the uveal tract, retina, vitreous, or optic nerve head. Typically affecting older people, intraocular lymphoma has also been described in young patients.9 Bilateral involvement is seen in about 80% of cases. Although several types of intraocular lymphoma have been recognized, large cell lymphoma is the most common one. Intraocular lymphoma is generally of the B-cell type, similar to NHL elsewhere in the body, whereas T-cell lymphoma is quite rare.3

Malignant lymphoma is usually a systemic disease affecting multiple organs. Occasionally, intraocular involvement may be the initial manifestation of the systemic disease. Two different forms of NHL can affect the eye: the CNS type and the systemic (lymph node–visceral) form. Intraocular lymphoma affecting only the eye is rare. The intraocular involvement can be divided into 2 general types of disease. The first is vitreoretinal lymphoma and is the most common form; it is found in association with CNS lymphoma, which is usually of the B-cell type.1 The second is uveal lymphoma, which is associated with visceral or nodal involvement. In the early stages the disease may assume one of these 2 variations, but in more advanced stages they may overlap considerably.10

Ocular signs and symptoms of lymphoma may occur before the onset of systemic or CNS manifestations. In NHL of the CNS, the presence of vitreous cells masquerading as vitritis is the most common ocular finding, followed by an anterior uveitis–like picture and subretinal yellow infiltrates. At the time of intraocular appearance, CNS involvement is seen in 60% of patients.

Diagnosis of ocular lymphoma with CNS involvement requires a sampling of the vitreous or subretinal space and identification of malignant lymphocytic cells. With the use of immunohistochemical stains, the type of lymphoma can easily be defined. Although primary intraocular lymphoma cells have been identified by histopathologic diagnosis in the iris, ciliary body, and optic nerve in a few patients, lymphoma in these sites has rarely been observed clinically.2

The mechanism allowing uveal invasion by lymphoma cells remains unknown. Hematogenous spread should be considered. Previous histopathologic reports demonstrate a perivascular distribution of malignant cells in the iris,11 supporting this possibility. Velez et al12 have proposed that long-standing aggressive tumors of the posterior segment break through the Bruch membrane and invade the choroid, thus gaining access to the anterior uveal structures.

In our patient, the iris, ciliary body, and anterior choroid were initially the only sites of lymphomatous involvement. The vitreous of the left eye was infiltrated during a second exacerbation of the disease. Our case is a rare, T-cell NHL with an affinity for the anterior uvea and a later infiltration of the skin during chemo-

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Cases</th>
<th>Clinical Iris Involvement</th>
<th>Vitreous Cells</th>
<th>Cell Type</th>
<th>CNS or Systemic Lymphoma</th>
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<tr>
<td>Jensen et al3</td>
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<td>Yes (delayed)</td>
<td>T-cell</td>
<td>Skin</td>
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</tbody>
</table>

*CNS indicates central nervous system; RCS, reticulum cell sarcoma.
therapy, showing the aggressive nature of the patient’s disease.

Claudia Yalahalom, MD
Yossi Cohen, MD
Edward Averbubh, MD
Irene Anteb, MD
Gail Amir, MB, ChB
Jacob Pe’er, MD
Jerusalem, Israel

Corresponding author and reprints: Jacob Pe’er, MD, Department of Ophthalmology, Hadassah University Hospital, PO Box 12000, Jerusalem 91120, Israel (e-mail: peer@md2.huji.ac.il).


Pigmented Medulloepithelioma of the Ciliary Body

A 3-year-old girl developed leukocoria in her right eye and was found to have a fibrovascular ciliary membrane and a pigmented ciliary body mass. Following removal of the mass by iridocyclochoroidectomy and localized vitrectomy, it proved histopathologically to be a malignant medulloepithelioma with cytoplasmic melanin pigment. Five months later, tumor recurrence necessitated enucleation. Although ciliary body medulloepithelioma is usually an amelanotic, fleshy mass with an intrascleral cystic component, it can occur as a pigmented solid tumor that may resemble a melanoma or a neoplasm of the pigment epithelium.

Intraocular medulloepithelioma is a well-known but uncommon pediatric neoplasm that usually occurs in the ciliary body.1-4 This embryonic tumor is believed to arise from the primitive medullary epithelium that composes the anterior lip of the optic cup.2 It usually occurs on the ciliary body of a young child as a fleshy gray or pink mass, often with clinically evident cysts. Although small amounts of pigment occasionally can be observed pathologically in the cytoplasm of medulloepithelioma cells, such pigmentation is not observed clinically.4 A pigmented medulloepithelioma in the central nervous system has been reported,5 but we are unaware of a clinically pigmented medulloepithelioma of the ciliary body. We report a clinicopathologic correlation of a malignant medulloepithelioma of the ciliary body that was intensely pigmented clinically and histopathologically.

Report of a Case. In July 1997, a 3-year-old white girl with a normal birth and medical history was noted to have intermittent exotropia and a white pupillary reflex in her right eye. Examination revealed a ciliary body mass and the patient was referred to the Oncology Service at Wills Eye Hospital. The right eye had a visual acuity of light perception and an intraocular pressure of 21 mm Hg. Following removal of the mass by iridocyclochoroidectomy and localized vitrectomy measured 11 × 8 × 6 mm. Microscopically it consisted of a scleral base, a pigmented superficial portion, and a nonpigmented deeper portion (Figure 3). The area that appeared pigmented grossly was composed microscopically of cords and tubules of well-polarized epithelium that was partially pigmented (Figure 3). The area was surrounded by a fibrous matrix containing spindle cells. Single, intensely pigmented cells, probably melanophages, were admixed with the neuroepithelial tubules (Figure 4). Corresponding to the less pigmented peripheral area seen grossly were spindle cells and tubules of nonpigmented epithelium set in a matrix of mucopolysaccharide

Pathologic Findings. On gross examination, the original tumor removed by iridocyclochoroidectomy measured 11 × 8 × 6 mm. Microscopically it consisted of a scleral base, a pigmented superficial portion, and a nonpigmented deeper portion (Figure 3). The area that appeared pigmented grossly was composed microscopically of cords and tubules of well-polarized epithelium that was partially pigmented (Figure 3). The area was surrounded by a fibrous matrix containing spindle cells. Single, intensely pigmented cells, probably melanophages, were admixed with the neuroepithelial tubules (Figure 4). Corresponding to the less pigmented peripheral area seen grossly were spindle cells and tubules of nonpigmented epithelium set in a matrix of mucopolysaccharide...
Figure 5) that stained positive for colloidal iron (Figure 6) and that was partially sensitive to hyaluronidase digestion. The pigment showed positive staining with the Fontana-Masson stain, confirming that it was melanin. Areas of the tumor contained a sarcomatoid arrangement of the cells, but no convincing skeletal muscle or cartilage was identified in the available sections. The tumor incorporated and encompassed the equatorial portion of fragmented lens tissue. The stroma of the pars plana was infiltrated by pigmented tumor cells. A few mitotic figures were present and the nuclei appeared pleomorphic and hyperchromatic. Tumor cells were present very close to one of the surgical margins. The final diagnosis was pigmented medulloepithelioma. It was classified as malignant on the basis of cytologic features, mitotic activity, and focal invasion of the ciliary body stroma.
mechanism containing cords of tumor. Often there is a fibrovascular cyclitic vitreouslike material may be present.

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hyaline cartilage, rhabdomyoblasts, nonteratoid medulloepithelioma is a pure neoplastic proliferation of cells neoplastic proliferation of cells. Intraocular medulloepi-
thelioma. No heteroplastic elements were identified. The main diagnosis was recurrent or residual pigmented medulloepithelioma.

Comment. Intraocular medulloepi-
thelioma is a rare embryonic neo-
plasm that usually is diagnosed in the first decade of life as a ciliary body mass. It can be classified as benign or malignant and as teratoid or non-
teratoid. Histopathologic criteria for malignancy include the presence of undifferentiated areas that resemble retinoblastoma or sarcoma and local invasiveness. Metastasis is very rare and usually occurs in cases with extracocular extension. In 2 reported series the tumor was classified as ma-
lignant in 66% and 90%. The nonteratoid medulloepithelioma is a pure neoplastic proliferation of cells that resembles the medullary epithelium without heteroplastic elements, whereas the teratoid variant contains heteroplastic elements like hyaline cartilage, rhabdomyoblasts, striated muscle, and neural tissue re-
sembling brain. The tumor in our patient was a malignant teratoid medul-
loepithelioma.

Clinically, ciliary body medullo-
epithelioma is usually a fleshy pink le-
sion. Large cystic spaces that contain vitreouslike material may be present. Often there is a fibrovascular cyclitic membrane containing cords of tumor cells. The medulloepithelioma in our patient was unusual in that it was deeply pigmented clinically and histopathologically and lacked a cystic component. A pigmented medulloepi-
thelioma of the central nervous sys-
tem has been reported as a tumor in the fourth ventricle in a 9-year-old boy. We are aware of one other case of clinically pigmented medulloepi-
thelioma of the ciliary body. It occurred in an 18-year-old African woman who had a black epibulbar mass and expansive hemorrhage. Hence, the appearance of that ciliary body medulloepithelioma was quite different from the one seen in our case. Although most medulloepitheliomas lack pigment clinically, a few melanin granules are sometimes observed microscopically in ciliary body medulloepitheliomas.

Our case showed findings con-
sistent with other reported malignant medulloepitheliomas, except that the cytoplasm of many of the neuroectoder-
cellular elements were identified. The main diag-

J. A. Shields, MD

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phia (Dr Eagle).

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A. K. Samad, MD, and Edward J. Doherty, OD, assisted in the care of
the patient. Lorenz E. Zimmerman, MD, and Ian W. McLean, MD, reviewed the histopathologic sections and concurred with the diagnosis.

Reprints not available from the authors.


**Endogenous Nocardia asteroides Endophthalmitis**

*Figure 1.*

*Nocardia asteroides*, a Gram-positive, aerobic, soil-borne bacterium, is a cause of opportunistic infections in immunocompromised patients, particularly those with lymphoreticular neoplasms, long-term pulmonary disorders, and long-term steroid use. The organism is usually inhaled and may cause localized or disseminated infections. A predilection for its spread to the brain and soft tissues has been noted. Suppurative necrosis and abscess formation is the pathologic hallmark. Nocardia is distinguished by beaded, branching, filamentous growth in purulent exudate and tissue sections.

Ocular involvement by *Nocardia* is very rare, with approximately 30 cases of intraocular nocardial infection reported in the literature. Optimal therapeutic regimens are not established. Only 2 reports detail expeditious and tissue sections.

The following day, visual acuity declined to 20/100 OD and 2+ anterior chamber cell and 3+ vitritis were present. Vitreous tap was performed and samples were sent for bacterial and fungai cultures and mycobacterial stains. A tuberculin skin test was performed. Serologic tests for herpes simplex and varicella zoster viruses, cytomegalovirus, and syphilis were performed. The patient was treated with 5 µg of intravitreal am-
photerocin B and intravenous amphotericin B for presumptive fungal endophthalmitis. The oral prednisone was tapered.

The patient was observed for 1 week, with no improvement. Bronchoscopic and transthoracic needle biopsies of the lung lesion were attempted but histopathologic test results disclosed inflammation only, with no tumor or organisms present. A wedge resection of the lung lesion was subsequently performed.

One week after initial intravitreal injection, visual acuity had declined to hand motions OD. A relative afferent papillary defect was present in the right eye. The ocular lesion now appeared to involved much of the macula and optic disc, although it was difficult to view because of dense vitritis. All cultures and serologic test results were negative at this time. A second intravitreal injection of 5 µg of amphotericin B was administered.

Pars plana vitrectomy with retinal and subretinal biopsy were performed 10 days after the initial ocular examination. Intraoperatively, a large yellowish mass was present inferotemporally and extended to within 1 disc diameter of the fovea. Subretinal fluid was present throughout the macula. Neutroretinitis was present and extended from the optic disc along the superior and inferior temporal arcades. During biopsy, the subretinal tissue was noted to be extremely firm in consistency. Intravitreal vancomycin (1 mg) and ceftazidime (2 mg) were injected at the end of the procedure followed by fluid-gas exchange.

Eleven days after initial ocular presentation, examination of the lung specimen disclosed filamentous organisms. Thirteen days after presentation, the culture of the lung tissue was positive for N asteroides (ie, at 8 days of growth). The patient began taking oral trimethoprim-sulfamethoxazole. Based on sensitivity data, the eye was injected intravitreally with 25 µg of imipenem and 200 µg of amikacin (doses were adjusted downward to account for the 50% air bubble in the vitreous). Cultures of the vitrectomy specimen became positive at 4 days of growth and organisms consistent with Nocardia species were noted on transmission electron microscopy of the subretinal biopsy.

Postoperatively, no view of the posterior segment was possible. Echography performed 1 week after surgery disclosed an extensive shallow retinal detachment with enlargement of the lesion. Surgical repair was considered but was not performed due to the patient’s anesthesia risk.

A 4-mm-diameter ring-enhancing lesion of the left temporal lobe was noted on a brain magnetic resonance imaging scan, which was considered to be a small abscess (Figure 2). The lesion remained stable during treatment. The patient was discharged 3 weeks after admission due to improvement in his systemic condition. Long-term oral tri-
Histopathologic examination of the lung biopsy specimen revealed bronchopneumonia with occasional clusters of filamentous organisms with the silver stain (Figure 4). Examination of the enucleated eye disclosed iris neovascularization, cicatricial membrane, detachment of the retina with extensive subretinal proliferation, a serosanguinous subretinal effusion, rare foci of lymphocytes in the choroid, and no microbial organisms.

Comment. Endogenous *N. asteroides* endophthalmitis is associated with dismal outcomes, with many eyes progressing to blindness despite treatment. The primary site of infection is most often in the lung. Patients may have features of anterior or posterior uveitis. Symptoms include floaters, decreased vision, pain, and photophobia. Chorioretinitis with subretinal abscess formation is the hallmark of endogenous nocardial endophthalmitis. Exudative retinal detachment may occur. Typically, organisms are located under the retinal pigment epithelium or in the subretinal space and may proliferate along the Bruch membrane.

*Nocardia* infections may be difficult to diagnose. Organisms can be identified on Gram, acid-fast, and Gomori methenamine silver stains. *Nocardia* organisms grow readily on most nonselective media and typical colonies are usually seen after 3 to 5 days. Cultures and smears are positive in only one third of cases. Retinal and subretinal biopsies were performed in this case because of diagnostic uncertainty. Electron microscopic examination of the subretinal biopsy was successful in demonstrating organisms.

The treatment of ocular nocardial infection has been met with limited success, although favorable outcomes are common for infections at nonocular sites. The role of vitrectomy in nocardial endophthalmitis is uncertain. We injected amikacin and imipenem intravitreally in our patient. Although toxicity data are limited for imipenem, it displays comparable efficacy to intravitreal vancomycin in experimental *Bacillus cereus* endophthalmitis, and to amikacin in experimental *Pseudomonas aeruginosa* endophthalmitis. We chose to administer intravitreal imipenem in light of these data, known nocardial sensitivity and synergy data, and the patient’s deteriorating ocular condition. A course of intravenous ceftriaxone was also added for the above reasons. Despite these measures, phthisis ensued in our patient.

Sulfonamides remain the antibiotic of choice for *Nocardia* elsewhere in the body. Trimethoprim-sulfamethoxazole is the preferred formulation by most clinicians despite increased myelotoxicity with this combination. In vitro synergistic activity has been demonstrated against most isolates. The variable and chronic course of nocardiosis necessitates long treatment durations (6-12 months). Alternative regimens are largely based on in vitro susceptibilities and efficacy in animal models, and include amikacin and imipenem and other combinations.

Eugene W. M. Ng, MD
Ingrid E. Zimmer-Galler, MD
W. Richard Green, MD
Baltimore, Md

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Corresponding author: W. Richard Green, MD, Eye Pathology Laboratory, The Johns Hopkins Hospital, Maumenee 427, 600 N Wolfe St, Baltimore, MD 21287.


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Neuroblastoma Within a Congenital Orbital Teratoma

Congenital orbital teratomas are rarely malignant. In fact, a total of 4 prior reports exist in the literature describing malignant orbital teratomas, and only 2 of these describe the nature of the malignant cells. We report a case of a congenital orbital teratoma containing foci of neuroblastomatous elements confirmed by immunohistochemical techniques. Given that the tumor was noninvasive and no systemic involvement was discovered, no further treatment was undertaken. Two years following the operation, the patient remained free of tumor in the orbit and at other sites. A review of the literature concludes that similar cases should be handled by complete excision, and further therapy should be based on the pathological findings of the individual case.

Teratomas are generally benign congenital growths, which by definition consist of derivatives from each of the 3 germ-cell layers. They are most commonly found in the gonads, but they may develop ectopically in cervical, mediastinal, sacrococcygeal, intracranial, and orbital locations. Primitive neuroectodermal tissue has long been known to be associated with teratomatous tissue in both intracranial and ovarian sites. One report found a neuroblastoma within a teratocarcinoma.

Primary congenital teratomas of the orbit are uncommon and rarely malignant. Four prior reports describe malignant orbital teratomas. One case was primarily an intracranial teratoma involving the optic nerve. Another report had no description of the nature of the malignant cells. Garden and McMahon described a case in which the malignant cell population appeared 3 years after the excision of a benign orbital teratoma and consisted of cells believed to be a malignant germ cell tumor. An orbital teratoma with neuroblastic and rhabdomyoblastic elements has also been documented. We report a case of orbital teratoma with malignant neuroblastomatous features.

Report of a Case Clinical History. The patient was the product of an uncomplicated pregnancy and was born at full term via normal abdominal delivery. She was initially seen at age 5 weeks for the evaluation of congenital and increasing proptosis of her left eye. At that time, grossly she had +4.00 +3.00 OD and +14.00 +3.00 × 85 OS. The right fundus was unremarkable, while the left showed chronic papilledema characterized by a pale halo of edema around the disc. An orbital computed tomography scan showed a septated intracranial mass with calcifications that had increased in size from the previous magnetic resonance imaging findings, and had extended into the lacrimal fossa (Figure 1). The orbital rim was expanded and thinned, but there was no osseous destruction. The orbital tumor was excised by a left lateral orbitotomy.

Histopathology. The specimen consisted of 3 pieces of tissue, the largest measuring 30 × 19 × 9 mm. The specimen was bisected, and examination revealed areas of a serosalike surface. In addition, there was one cystic area filled with gelatinous material and hair. Another area was firm and gray, suggestive of cartilage.

Microscopic examination revealed a complex cystic structure lined partially by pseudostratified ciliated columnar epithelium and partially by keratinized stratified squamous epithelium. There were adnexal structures in the portion of the wall lined by the squamous epithelium. The cyst was filled with keratinous debris. Adjacent to the cyst was a well-circumscribed cartilaginous structure. In addition, there was mature central nervous system tissue present. In one focal area associated with the central nervous system tissue, there was a focus (measuring 5 × 4 mm) of undiff-
entiated, small, round cells with modest amounts of eosinophilic cytoplasm (Figures 2 and 3). The chromatin of the cells was moderately condensed, and there were occasional small nucleoli. There was 1 mitosis in 20 high-power fields. There were no rosettes present.

Paraffin-embedded sections were stained using an immunoperoxidase technique. The small, undifferentiated cells displayed negative immunoreactivity with keratin, CD99 (product of MIC2 gene, positive in glioblastoma, ependymoma, Ewing sarcoma, and acute lymphoblastic leukemia), and vimentin. There was positive immunoreactivity with neuron-specific enolase (Figure 4) and synaptophysin. The pattern of reactivity was consistent with neuroblastoma, and would be unlikely in any of the morphologic differentials in this case, which include leukemic infiltrates, Ewing sarcoma, primitive neuroectodermal tumor, and Wilms tumor.

Comment. The intriguing aspect of this case was the presence of immature cells consistent with neuroblastoma in an otherwise typical orbital teratoma. The presence of these cells raised interesting questions in the subsequent management of the patient. Some authorities feel that the presence of immature cellular components should not be taken as evidence of malignancy. However, the prognosis of central nervous system teratomas is worse for the immature teratoma than for the mature teratoma, and dissemination of tumor cells systemically and in cerebrospinal fluid has been documented in immature intracranial teratomas.

Mayberger et al, in a report on a benign cystic teratoma of the ovary with neuroblastomatous change, suggested that if the teratoma is noninvasive, without metastasis, then removal alone is adequate. This suggestion relies on the theory that the primitive neuroectodermal tissue within the teratoma is derived from ectodermal germ cells and not from mature neural tissue, which developed into undifferentiated tissue. However, a separate study warned that the clinician must be aware that on occasion, primary neuroectodermal tumors arise ectopically in the ovary, along with teratomatous tissue. These latter tumors are known to metastasize, with the risk increasing as the degree of differentiation of the neuroectodermal tissue decreases. The same study suggested that tumors with endodermal and mesodermal features along with primitive neuroectodermal tissue may be classified and treated as benign teratomas, while those with massive, confluent growth of neuroectodermal tissue and little of the other 2 germ layers may be primary malignant tumors.

Ulbright et al argue that treatment should be individualized depending on the type of non–germ cell tumor involved, speculating that some forms of non–germ cell malignancies (specifically leiomyosarcoma, nephroblastoma, neuroblastoma, and giant cell tumor), when found within teratomas, may not affect the prognosis. As a result, they argue that such tumors should be called “non-germ cell malignancy in teratoma” and advocate treatment of the growth as a benign teratoma with complete resection. The results of their study further indicate that the role of chemotherapy is questionable in such tumors.

The management of this case was discussed at the Pediatric Tumor Board. Based on the above considerations, this tumor was classi-
fied as an immature teratoma containing neuroblastomatous elements. The tumor had been completely excised, and no other treatment was undertaken. The child has been followed up for 2 years and has no evidence of recurrent orbital tumor or neuroblastoma at other sites.

In conclusion, orbital teratomas may rarely contain non-germ cell malignancies. The initial clinical management of these cases should be complete excision. Decisions regarding adjunctive chemotherapy or radiation therapy should be based on the pathologic findings for the individual case.

David J. Wilson, MD  
Roger A. Dailey, MD  
John L. Wobig, MD  
Portland, Ore  
Jason W. Dimmig, BA  
Burlington, Vt

Corresponding author and reprints:  
David J. Wilson, MD, 3375 SW Terwilliger Blvd, Casey Eye Institute, Portland, Ore 97201-4197 (e-mail: wilsonda@ohsu.edu).


**Substance P, Insulinlike Growth Factor 1, and Surface Healing**

Impaired adhesion, migration, and/or mitosis can compromise corneal epithelial healing. Persistent epithelial defects can progress to ulceration, perforation, or endophthalmitis. Currently, our options are limited to methods that address the underlying cause of the epithelial defect. In addition to addressing exposure keratopathy, mechanical irritation to the eye, and systemic diseases, clinicians must consider the tear film, minimize the mechanical aspects of delayed wound healing, and use collagenolytic enzyme inhibitors. Specific therapy includes preservative-free artificial tears, pressure patching, bandage contact lens, and N-acetylcysteine. The recent use of nerve growth factor, amniotic membrane transplantation, and scleral lens has been reported. Non-surgical therapeutic options have limited effect, and surgical procedures such as lamellar or penetrating keratoplasty become necessary to preserve the anatomic integrity of the globe. Vision-threatening procedures (Gunderson flap, tarsorrhaphy, evisceration, or enucleation) may also become necessary.

Recently, growth factors, neuropeptides, and fibronectin have promoted epithelial wound healing. Topical substance P (SP) and insulin-like growth factor 1 (IGF-1) circumvented surgical intervention in this case.

**Report of a Case.** A 79-year-old monococular woman with a persistent epithelial defect following penetrating keratoplasty in the left eye visited the University of Wisconsin (Madison) Cornea Service for consultation.

Her medical history was significant for Fuchs endothelial dystrophy, cataracts, and primary repair of a traumatic ruptured globe with subsequent evisceration of the right eye. In her pseudophakic left eye, penetrating keratoplasty was performed. A small suture tract leak and a small epithelial defect associated with a trace graft override were present on the first day following surgery. The suture tract leak healed quickly.

The defect persisted despite discontinuing polymyxin B sulfate, adding erythromycin, and reducing the frequency of 1% prednisolone. Four postoperative months of artificial tears, pressure patching, bandage contact lens, autologous serum combined with artificial tears, and anterior stromal micropuncture were ineffective at healing the defect.

The defect and the threat of complications persisted. At consultation, her pinhole visual acuity was 20/80 OS; medications included erythromycin and 0.2% brimonidine tartrate for ocular hypertension. The anesthetic epithelial defect measured 1.0 × 2.0 mm (Figure 1). The sutures were intact. Graft override still occurred adjacent to the epithelial defect.

This elderly monocular woman was offered an option of vision-correction.
threatening surgical procedures or topical SP with IGF-1. The patient understood the investigational and compassionate-use nature of SP and IGF-1. Informed consent was obtained.

Sterile SP (250 µg/mL) and IGF-1 (1.0 µg/mL) were prepared, dispensed, refrigerated, and discarded after 1 week. One drop of each compound was administered every 15 minutes for 2 hours each morning and night for the first week. Polymyxin B and brimonidine were continued. This treatment frequency was chosen on the basis of in vitro data (Christopher J. Murphy, DVM, PhD oral communication, January 2001), suggesting a persistent trophic effect after 2 hours of cellular contact with SP.

Complete healing occurred within 1 week (Figure 2). Symptomatic itching was mild and temporary. Her epithelium remained intact during a 2-week taper of SP and IGF-1 administration. Polymyxin B and both SP and IGF-1 were discontinued at the end of the second and third weeks of treatment, respectively. Her epithelium remained intact on follow-up examination at 3 weeks after discontinuing therapy, and it has remained healed without epithelial breakdown throughout the ensuing 8 months.

Comment. Our armamentarium for corneal epithelial wound healing is limited. The trigeminal nerve and the neuropeptide it releases, SP, contribute to the maintenance of healthy corneal epithelium. Substance P has been shown to be synergistic with IGF-1 in the promotion of cellular processes conducive to wound healing.

Three reported cases describe the complete resurfacing of persistent epithelial defects in human corneas in response to SP used synergistically with IGF-1. Our patient responded to this therapy and did not require surgical intervention, suggesting a therapeutic advantage of this combined therapy. Our case, collectively with those cited, demonstrates the need for prospective clinical trials to declare the clinical value of this treatment modality in preventing the devastating consequences of nonhealing epithelial defects.

Catherine H. Lee, MD
Amanda L. Whiteman, DVM
Christopher J. Murphy, DVM, PhD
Neal P. Barney, MD
Madison, Wis
Peter B. Taylor, MD
Fond du Lac, Wis
Ted W. Reid, PhD
Lubbock, Tex

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Corresponding author and reprints: Neal P. Barney, MD, Department of Ophthalmology and Visual Sciences, University of Wisconsin, 2870 University Ave, Suite 206, Madison, WI 53705 (e-mail: npbarney@facstaff.wisc.edu).

4. Lee S, Tseng SCG. Amniotic membrane transplantation for persistent epithelial defects with...
Cerebral cavernous malformations (CCM) are defined by abnormally enlarged capillary cavities without intervening brain parenchyma. Clinical symptoms include seizures, hemorrhage, and focal neurological deficits. Their prevalence is close to 0.5% in the general population. Familial forms are increasingly recognized. Three CCM loci were mapped to chromosomes 7q (CCM1), 7p (CCM2), and 3q (CCM3). KRIT1, a protein of unknown function, was recently identified as the mutated protein in families with the CCM1 gene.1

Cavernomas have been observed in other organs such as the retina. We report what is to our knowledge the first observation of a KRIT1 mutation in a patient with retinal and cerebral cavernous angiomas.

Report of a Case. A 34-year-old woman was followed up for recurrent herpetic keratitis of the left eye. A fundus examination and retinal angio-

grams of the same eye showed a peripheral retinal vascular lesion, characteristic of a cavernous angioma (Figure 1 A and B). The lesion had first been observed when the patient was 11 years old. The right fundus was normal. Her visual acuity between episodes of keratitis was 20/20 OU. There was no other eye abnormality. From 1995 to 1999, we did not observe any change of the retinal cavernoma. Results of dermatological and neurological examinations were normal. Brain magnetic resonance imaging showed 4 cavernomas (Figure 1C). Five relatives of the patient were also known to have cerebral cavernomas. We could not perform ophthalmological examinations on these subjects because they live in another country.

Sequencing of exon 10 of the KRIT1 gene in our patient revealed a heterozygous insertion of cytosine after nucleotide 1374 that

![Figure 1. A, Fundus examination of the left eye showing a localized peripheral cluster of saccular whitish to dark red aneurysms of various sizes. B, The same lesion was observed using fluorescein angiography. The adjacent vessels were normal, and there was no sign of leakage. C, Magnetic resonance imaging (1.5 T, T2-weighted imaging axial sequences) showing a cerebral cavernoma close to the right ventricle (white arrow), seen as a mixed hypointense and hyperintense signal.](https://archophth.jamanetwork.com/"")
caused a frameshift leading to a premature stop codon (Figure 2), and therefore a truncated protein. This mutation was not detected in a panel of 50 healthy controls. The DNA sequence of the complete gene was determined, and no other mutation was found.

Comment. Retinal cavernomas are rare and usually asymptomatic. The largest series reported so far consists of 9 cases.3 Most reports are of sporadic retinal cavernomas with no associated neurological disease. The occurrence of retinal and familial brain cavernomas has seldom been described.3,4 In the absence of a systematic fundus examination, retinal cavernomas could be undiagnosed in patients with brain cavernomas. In rare cases such as that described in this report, the diagnosis of retinal cavernomas can lead to the detection of asymptomatic cerebral cavernomas.

The vascular nature of the lesions observed in the retina and brain as well as the cosegregation of both types of lesions strongly suggest that the occurrence of these 2 conditions is not coincidental. Interestingly, the mutation observed in our patient is similar in nature to those observed in families with CCM; namely, mutations leading to a truncation of the C-terminal part of KRIT1.3 Because the insertion of a cytosine at nucleotide 1374 has not previously been reported, we can not exclude the possibility that this mutation is associated specifically with the occurrence of both retinal and cerebral lesions. In this article, we show for the first time that a mutation in KRIT1, a gene known to exist in most families who have CCM with isolated brain cavernomas, is present in a patient with both retinal and brain cavernomas. Another mutation in the KRIT1 gene was recently found in one family characterized by the cosegregation of cutaneous and brain cavernomas.5 These results strongly suggest that these lesions are underlaid by a common mechanism and that KRIT1 plays an important role in cutaneous, retinal, and cerebral vascular development.

Sophie Laberge-Le Couteulx, MD
Antoine P. Brézin, MD
Bertrand Fontaine, MD, PhD
Elisabeth Tournier-Lasserve, MD
Pierre Labauge, MD
Paris, France

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Corresponding author: Pierre Labauge, MD, Faculté de Médecine Lariboisière, Laboratoire de Génétique des Maladies Vasculaires, 10 Avenue de Verdun, EPI 99-21, 75010 Paris, Cedex, France (e-mail: labauge@hotmail.com).


Retinal Alterations in Acquired Partial Lipodystrophy: A Case Report

Acquired partial lipodystrophy (PLD) is an uncommon disorder of unknown cause, usually affecting women, characterized by the loss of subcutaneous adipose tissue of the upper half of the body, including the face. Persistent low C3 serum levels and normal serum levels of C1q,
C4, and C2, the early reacting components of the classic pathway, are frequently found in these patients. The presence in the patient’s serum of the C3 nephritic factor, an immunoglobulin G antibody that stabilizes the alternative C3 convertase, suggests C3 activation via the alternative pathway. These complementary abnormalities may occur without renal disease.

Ocular complications of PLD have been described only in case reports. They are characterized by the presence of yellow, drusen-like lesions at the posterior pole and are always associated with type II mesangiocapillary glomerulonephritis.

Report of a Case. A 38-year-old white woman with a 10-year history of progressive facial wasting was referred 36 months earlier to the outpatient service of clinical immunology for symptoms of arthralgia, myalgia, and morning stiffness, unsuccessfully treated with nonsteroidal antiinflammatory drugs. Results of physical examination showed the characteristic appearance of PLD localized to the face (Figure 1) with skin hyperpigmentation, normal muscular tone, and trophism. There was no evidence of arthritis or signs of visceral involvement.

Laboratory examination results showed normal erythrocyte sedimentation rate, white and red blood cell counts, levels of blood glucose (<100 mg/dL [<5.6 mmol/L]), blood urea nitrogen (30-46 mg/dL [10.7-16.4 mmol/L]), and serum creatine (<1.10 mg/dL [<97.2 µmol/L]), creatinine clearance rate (80-110 mL/min [1.3-1.8 mL/s]), and urinalysis results. Normal plasma levels were found for muscle enzymes, thyroid hormones, adrenocorticotropic hormone, and cortisol. All of these results remained normal after a 3½-year follow-up examination. The patient tested negative for antinuclear autoantibodies and positive for rheumatoid factor (serum level, 40-160 IU/mL). Serum complement components showed very low levels of C3 (3.0-4.5 mg/dL [normal value, 80-170 mg/dL]) and normal levels of C1q, C4, and factor B. The assay for alternative C3 nephritic factor was positive. Since no signs of renal disease, either clinical or serological, were observed throughout the 3 years of follow-up, a renal biopsy was not performed. Despite 1-year treatment with hydroxychloroquine, no significant changes in joint symptoms were reported by the patient.

A routine ophthalmic examination was carried out 11 months after hydroxychloroquine treatment. Visual acuity was 20/20 OU, the anterior segment and lachrymal secretion did not show any pathological change, and the intraocular pressure was normal. The fundus examination revealed a large number of drusen-like lesions at the posterior pole and midperiphery that were round, discrete with defined borders (some were confluent), and of different sizes, the larger located at the posterior pole. The drusen-like lesions were more numerous in the nasal quadrants of the retina but larger in the temporal areas. Fluorescein angiography results demonstrated that all of the lesions had early hyperfluorescence, which remained unchanged throughout the examination, showing the characteristics of small hard drusen. The central fovea revealed normal pigmentation (Figure 2).

Color vision was normal. Visual field examination showed decreased central sensitivity in both eyes, with an enhancement of the
blind spot. Electroretinogram results and visual evoked potentials were normal, while the electro-oculogram results revealed a pathological result in both eyes, with an Arden index of 120. This situation remained unchanged at a 25-month follow-up.

A study was also carried out on her living relatives: 2 daughters, her sister, her brother, and his 3 sons. None of them showed signs of the disease or complement abnormalities.

Comment. Partial lipodystrophy is a rare disease characterized by an involvement of the subcutaneous fat tissue. A high percentage (65%-70%) of patients with PLD have low serum levels of C3 and normal serum levels of C1q, C4, C2, and B factor. These findings indicate the activation of the complement cascade through the alternative pathway, due to the presence in the serum of the nephritic factor, an immunoglobulin G antibody that stabilizes the alternative C3 convertase, with consequent continuous consumption of C3. This immunoglobulin G was found to be associated with a membranoproliferative nephritis, known as type II mesangiocapillary glomerulonephritis. This association is not constant; in fact, it was described that patients with PLD who were positive for nephritic factor did not develop nephropathy; on the other hand, the nephritic factor was also found, although rarely, in the serum of subjects in good health.

Retinal and renal lesions develop at the interface between convolute microvessels, such as those of the choriocapillaris and glomerulus, and a basement membrane structure. Under this aspect, the role of highly permeable vessels in the pathogenesis of such lesions could be hypothesized. Eye involvement is rare in PLD and has always been found in patients with renal impairment.

The case we reported is, to our knowledge, the first with ocular involvement in PLD without impairment of renal function. Whether the nephritic factor plays a direct role in the pathogenesis of retinal lesions is not conclusive since an ocular examination of normal subjects with serum nephritic factor has not been reported to our knowledge.

Although the retinal lesions do not seem to be site-threatening, an ophthalmic examination should be performed in patients with PLD, even in the absence of renal function impairment, to have a complete clinical picture.

Pasquale Aragona, MD, PhD
Paolina Quattrocchi, MD
Costantino J. Trombetta, MD
Eduardo Ferlazzo, MD
Rosaria Spinella, MD
Domenica Bonanno, MD
Messina, Italy

Corresponding author and reprints: Pasquale Aragona, MD, PhD, Viale Boccetta 70, I-98122 Messina, Italy (e-mail: p_aragona@hotmail.com).


Exercise-Induced Vasospastic Amaurosis Fugax

Amaurosis fugax is characterized by a sudden, monocular, painless, temporary visual loss due to a hypoperfusion of retinal circulation. Some of the more frequent causes include atheromatous disease of the internal carotid or opthalmic artery, vasospasm, optic neupropathies, giant cell arteritis, angle-closure glaucoma, increased intracranial pressure, orbital compressive disease, a steal phenomenon, and blood hyperviscosity or hypercoagulability. Vasospasm may account for many cases of unknown cause. Amaurosis fugax due to exercise-induced vasospasm has been described only once, in 1989 by Imes and Hoyt. They described 6 healthy young adults who experienced visual loss precipitated by exercise. Three of them had monocular visual loss.

Exercise-induced visual disturbances not due to a hypoperfusion of retinal circulation include pigmentary glaucoma attacks, which may be painless, Uhthoff symptom after optic neuritis, and unformed hallucinations secondary to occipital lobe tumors. We describe 3 more patients with exercise-induced monocular transient visual loss, probably caused by vasospasm.
Report of Cases. Case 1. For 5 years, a 65-year-old man experienced recurrent exercise-induced transient monocular blindness. Visual symptoms consisted of a rapid progressive visual field constriction in his right eye. If the patient did not stop exercising, complete monocular blindness would occur. The events lasted from 30 seconds to 3 hours. They regularly appeared during heavy sport activities such as jogging or biking. During the 5 years, the frequency and strength of the attacks continuously decreased. The patient was in excellent health, had participated in sports regularly since his youth, and had no coronary risk factors. He had no history of migraine. He underwent an extensive work-up that included a neuro-ophthalmologic examination (with a gonioscopy), computerized visual field testing, visual-evoked potentials, a general and cardiovascular clinical examination, echocardiography, Holter monitoring, magnetic resonance angiography, and transcranial and transorbital Doppler and duplex ultrasonography. The results were normal. Blood evaluation included a complete blood cell count, blood chemical analyses, blood coagulation studies, and tests for thyroid function, erythrocyte sedimentation rate, antinuclear antibodies, cryoglobulins, syphilis, Lyme disease, and antecardiolipin antibodies. Because the patient was regularly able to provoke such episodes by climbing stairs, we had the opportunity to examine the patient several times during an attack. We could use fundus photography to observe the right central retinal artery (Figure). A Doppler ultrasonographic study during an attack showed a transient stopping of blood flow in the central retinal artery. We never observed a relative afferent pupillary defect during an attack. Treatment with aspirin or nifedipine had no effect.

Case 2. A 40-year-old physician saw us because of a single attack of a hemianopic temporal scotoma in the left eye that had occurred during heavy physical activity. The episode lasted about 30 minutes. By covering 1 eye, he noticed that the defect was truly monocular. He had a history of migraine and had experienced headaches or stomachaches several times after heavy bodybuilding. He had undergone a work-up by internal medicine specialists for the stomachaches, which were diagnosed to be of vasospastic origin. Treatment with aspirin before sports participation reduced the degree of the symptoms. Results of a neuro-ophthalmologic examination and kinetic perimetry were completely normal. Because of the patient’s history of chronic exercise-induced migraine and stomachache, the ocular symptoms were considered by exclusion also to be caused by vasospasm, and no further examinations were carried out.

Case 3. For 14 years, a 45-year-old man experienced an exercise-induced transient “graying out” in his right eye lasting from 30 seconds to 15 minutes. Covering 1 eye confirmed that the symptoms were monocular. Results of a neuro-ophthalmologic examination, including a gonioscopy, were normal. Because this patient too was able to provoke such episodes by climbing stairs, we were able to examine him several times during an attack. We did not see any fundus abnormalities, possibly because stopping exercise resulted in a rapid recovery of visual acuity. However, immediate repeated automated perimetry after an attack showed a reproducible mild constriction of the visual field in his right eye. The left eye was always asymptomatic. A repeated intake of nifedipine resulted in the successful prevention of visual symptoms and a normal right automated perimetry finding after exercise. He had a history of thrombosis of the left superficial femoral artery. At the time of the examinations, the patient was not taking any medication. He had been smoking intermittently since he was a young adult. He had no history of migraine. The same blood work-up as in case 1 was performed, and results were found to be normal. Stress electrocardiographic findings were normal. Results of transcranial and transorbital Doppler and duplex ultrasonography were normal except for a slight hypoplastic right vertebral artery. Further work-up was refused by the patient.

Comment. Vasospasm is a recognized cause of amaurosis fugax and also occurs in elderly patients. Associated conditions include migraine, cluster headache, temporal arteritis, polyarteritis nodosa, and eosinophilic vasculitis.

Our 3 patients had exercise-induced monocular attacks, probably caused primarily by vasospasm. They illustrate the variety of transient monocular visual symptoms and findings that occur with exercise. Our first patient experienced rapid progressive visual field constriction. If exercising was not stopped, complete monocular blindness would occur. Anophthalmoscopy revealed a transient central artery occlusion (Figure). Our second patient noticed a hemianopic temporal scotoma in his left eye. The third patient described the
visual loss as “graying out.” Computerized perimetry performed immediately after an attack revealed an ipsilateral mild peripheral visual field constriction. In contrast to the 6 cases described by Imes and Hoyt,1 one of our patients with exercise-induced vasospasm had a late onset at age 60 years. Therefore, we conclude that vasospasm may also occur in elderly patients with a recent onset of exercise-induced amaurosis fugax.

Vasospastic amaurosis fugax is presumed to be caused by a vasospasm or reduced arterial flow.2,4 Vasospasms could be caused by a vessel hypersensitivity to certain vasoconstrictors released during physical exercise or by an inappropriate high release of such mediators (eg, catecholamines, endothelin-1, or neuropeptide Y). Winterkorn et al4 reported a successful treatment with calcium channel blockers. In our first patient, neither aspirin nor the calcium channel blocker nifedipine was able to reduce the severity of the attacks. Our second patient was able to reduce the stomachaches by taking aspirin before performing sports. Because he had had only 1 attack involving the visual system and was comfortable with aspirin intake, calcium channel blockers were not tried. In our third patient, nifedipine could successfully prevent attacks.

To our knowledge, this is the first report showing that the calcium channel blocker nifedipine may be effective in certain patients with exercise-induced vasospastic amaurosis fugax.

Andrea Jehn, MD
Barbara Frank Dettwiler, MD
Johannes Fleischhauer, MD
Matthias Sturzenegger, MD
Bern, Switzerland
Daniel S. Mojon, MD
St Gallen, Switzerland

Corresponding author and reprints: Daniel S. Mojon, MD, Department of Neuro-Ophthalmology and Strabismus, Kantonsspital, 9007 St Gallen, Switzerland (e-mail: daniel.mojon@kssg.ch).