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.

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 ocular 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 transflected for Southern blot hybridization. Briefly, the common sense primer for HPV types 16, 18, and 33 was 5'-AAGGGCGTAAACCAGAACATCGGT-3' and the antisense primers of each HPV strain were as follows: 5'-GTTTGAGCTCTGTCATA-3' for HPV 16, 5'-GTTGGTCGTCTCAGTCGACTCA-3' for HPV 18, and 5'-GTTCAATTGCTGGAC-3' for HPV 33. The hybridization probes were 5'-GATTTCATGCA-3' for HPV 16, 5'-TGAGAAACACAATACTATGGCGCGC-3' for HPV 18, and 5'-CATTAGGCTGACCTAGGCTGACGACTATG-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-
including 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 (venereal or genital warts), and mucocutaneous papillomas, which represent 7% to 12% of all conjunctival cutaneous papillomas, which represent 7% to 12% of all conjunctival cutaneous papillomas. 

Primary and secondary infectious human papillomavirus (HPV) types 16 and 18 are 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.

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.

Human papillomavirus type 33 is an uncommon genotype found in benign, dysplastic, and malignant lesions. In a study 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 study of eastern European women. Primarily found in anogenital lesions, recently HPV type 33 has been associated with breast cancer in Chinese and Japanese patients. Infection with HIV increases the risk for HPV-associated malignancy and may be a cofactor linking HPV infection and neoplasia. 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.

The effect of HAART in HIV-infected patients with HPV disease is unclear. Heard and coworkers attributed the reduced prevalence of cervical HPV lesions in HIV-positive men 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 studies 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. 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@nira .nci.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-methylenedioxymethamphetamine [Ecstasy]) and lysergic acid diethylamide. He denied intravenous drug administration. On examination, his visual acuity was 20/20 OD and 20/60 OS. Intraocular pressure readings were 10 mm Hg and 17 mm Hg, respectively. A biomicroscopic examination of the right eye demonstrated tiny white keratic precipitates and cells (+1) and flare (+1) in the anterior chamber (Figure 1). No synechiae were present, and the lens was clear. An examination of the left eye showed a hyperemic bulbar and perilimbal conjunctiva, white keratic precipitates, and cells (+4) and flare (+2) in the anterior chamber with a 2-mm hypopyon. The iris was bulging and was infiltrated by a whitish mass at the 6-o’clock position (Figure 2). 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 cytologic 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 reading 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-
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 clinically\(^3\)\(^7\)\(^8\), 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 al\(^2\) 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.\(^8\) 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, supporting this possibility. Velez et al\(^2\) 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 al(^3)</td>
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<td>CNS</td>
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<tr>
<td>Cooper and Riker(^4)</td>
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<td>No</td>
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<td>Lymph node–visceral</td>
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<td>Velez et al(^2)</td>
<td>1</td>
<td>Delayed (2 y later)</td>
<td>Yes</td>
<td>B-cell</td>
<td>CNS</td>
</tr>
<tr>
<td>Goldey et al(^1)</td>
<td>1</td>
<td>Primary</td>
<td>No</td>
<td>T-cell</td>
<td>Visceral</td>
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<tr>
<td>Coupland et al(^1)</td>
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<td>Delayed</td>
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<td>T-cell</td>
<td>Skin</td>
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\(^*\)CNS indicates central nervous system; RCS, reticulum cell sarcoma.
A 3-year-old girl developed leukocoria in her right eye and was found to have a fibrovascular cyclic 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.5 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. A pigmented medulloepithelioma in the central nervous system has been reported,6 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 18 mm Hg. A coincidental peripheral retinal temporal detachment was noted on visual field examination. The right eye was enucleated for diagnostic purposes. 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 18 mm Hg. A coincidental peripheral retinal temporal detachment was noted on visual field examination. The right eye was enucleated for diagnostic purposes.

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. The pigmented portion of the tumor measured 9 mm in diameter and 7 mm in thickness. The left eye had a visual acuity of 20/20 and was entirely normal.

Our clinical differential diagnosis included neoplasm of the ciliary body pigment epithelium, medulloepithelioma, melanocytoma, and melanoma. The parents were offered the options of enucleation, fine-needle aspiration biopsy, or local resection. They elected to have the tumor removed by local resection. A partial lamellar iridocyclochoroidectomy and localized vitrectomy were performed7 and it appeared that the entire mass was removed intact along with fragments of lens to which the tumor was adherent. Moderate bleeding from the cyclitic membrane occurred during tumor removal.

In September 1997, the patient was found to have a tractional retinal detachment in the affected eye and underwent a pars plana vitrectomy, lensectomy, and scleral buckling procedure with successful retinal reattachment. At the time of that surgery, however, a light tan mass was observed just superior to the area of the original tumor (Figure 2). The patient was referred to the Oncology Service and enucleation was performed. There is no local recurrence or metastasis 3 years postenucleation.

Pigmented Medulloepithelioma of the Ciliary Body

A 3-year-old girl developed leukocoria in her right eye and was found to have a fibrovascular cyclic 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.

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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.

Histopathologic study of the enucleated eye revealed the ex-
often there is a fibrovascular cyclitic fibrosis. Large cystic spaces that contain epithelium is usually a fleshy pink lesion. The patient was a malignant teratoid medulloblastoma, and neural tissue resembled those seen in the previously resected pigmented medulloepithelioma. No heteroplastic elements were identified. The main diagnosis was recurrent or residual pigmented medulloepithelioma.

**Comment.** Intraocular medulloepithelioma is a rare embryonic neoplasm 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 nonteratoid. 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 malignant 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 resembling brain. The tumor in our patient was a malignant teratoid medulloepithelioma.

Clinically, ciliary body medulloepithelioma is usually a fleshy pink lesion. 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 medulloepithelioma of the central nervous system 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 medulloepithelioma of the ciliary body. It occurred in an 18-year-old African woman who had a black epibulbar mass and expulsive 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 consistent with other reported malignant medulloepitheliomas, except that the cytoplasm of many of the neuroectodermal cells contained pigment. We do not believe that the tumor arose from the pigment epithelium because pigment epithelial tumors do not produce hyaluronic acid, which was present in our patient's tumor. Concerning the origin of the melanin pigment in our case, it is known that pigmentation can be present in other tumors of neuroectodermal origin, including ependymoma, cerebellar medulloblastoma, schwannoma, meningioma, and pigmented neuroectodermal tumor of infancy. Melanin pigment is also a transient feature in the fetal penile gland and is sometimes present in pinealoblastomas. Therefore, it is not surprising that melanin pigmentation may also occur in intraocular medulloepithelioma, which is also a neoplasm of neuroectodermal derivation.

The differential diagnosis of a pigmented medulloepithelioma includes ciliary body melanoma, neoplasm of the pigment epithelium of the ciliary body, melanocytoma, and iridociliary cyst. Ciliary body melanoma can occur in children and can appear very similar to the tumor in our case. However, the cyclitic membrane seen in our patient would be unexpected with a ciliary body melanoma. Adenoma of the pigment epithelium of the ciliary body occurs mostly in adult patients, but it can occasionally occur in children. The adenoma of the ciliary body pigment epithelium reported in a child by Campochiaro and associates12 was remarkably similar to our case in that it was a pigmented mass associated with a cyclitic membrane. Iridociliary cysts can appear pigmented, but they do not produce a cyclitic membrane and secondary cataract. Our case exemplifies the difficulties encountered in local resection of a ciliary body medulloepithelioma. Local surgical removal of this tumor is frequently complicated by extensive bleeding from the fibrovascular neoplastic cyclitic membrane. Recurrence is frequent because the tumor often grows as a thin sheet on the surface of ocular structures, which may be inapparent at the time of local tumor removal. Neoplastic cells can be left behind in the cyclitic membrane and enucleation often becomes necessary because of residual or recurrent tumor. Irridocyclectomy can be successful only for relatively small tumors that are not associated with an extensive neoplastic cyclitic membrane. Interestingly, this tendency for recurrence contrasts to acquired adenomas of the nonpigmented and pigmented epithelium of the ciliary body, which can often be completely removed by iridocyclectomy. In summary, we report the clinical and histopathologic features of a malignant medulloepithelioma of the ciliary body that was clinically and histopathologically pigmented. This unique variation of a rare neoplasm should be included in the differential diagnosis of pigmented lesions of the ciliary body.

Jerry A. Shields, MD
Ralph C. Eagle, Jr, MD
Carol L. Shields, MD
Arun D. Singh, MD
Philadelphia, Pa
Johane Robitaille, MD
Halifax, Nova Scotia

This study was supported by the Eye Tumor Research Foundation, Philadelphia, Pa (Drs C. L. Shields and J. A. Shields), the Award of Merit in Retina Research, Houston, Tex (Dr J. A. Shields), the Macula Foundation, New York, NY (Dr C. L. Shields), and the Noel T. and Sara L. Simmonds Endowment for Ophthalmic Pathology, Wills Eye Hospital, Philadelphia (Dr Eagle).

This study was presented at the combined meeting of the Armed Forces Institute of Pathology Ophthalmic Alumni Society, Theobald Society, and Hogan Society, Washington, DC, April 20, 2001.

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

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.4,5 Optimal therapeutic regimens are not established. Only 2 reports detail experiences with intravitreal antibiotics.6 We report our experience with a case of endogenous N asteroides endophthalmitis treated with vitreectomy and intravitreal and systemic antibiotics, and for which a diagnostic subretinal biopsy was performed.

Report of a Case. A 69-year-old man was admitted to our hospital with pleuritic chest pain, chronic fatigue, weight loss, and a left upper lobe lung mass on computed tomography, which was judged to be a malignant or infectious process. The patient had glomerulonephritis with renal failure and had received oral prednisone for 16 months. Ocular history was unremarkable.

During admission, the patient reported having 2 days of floaters in the right eye. No pain or photophobia was present. Examination disclosed visual acuity of 20/30 OD and 20/20 OS. Pupils, visual fields to count fingers, color-plate test results, and tensions were normal. Slitlamp examination disclosed mild cataracts in both eyes. Ophthalmoscopy of the right eye disclosed 2+ vitritis and an elevated mass 3 disc diameters in size inferotemporal to the fovea within the vascular arcade (Figure 1). The lesion was yellowish with hemorrhages on the surface. The disc was unremarkable. Ophthalmoscopy findings of the left eye were unremarkable.

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 fungal 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-

Figure 1. A, Ophthalmic appearance of the optic nerve head and subretinal abscess in the temporal area of the macula. B, Yellowish appearance of the subretinal abscess with overlying retinal hemorrhages. Moderate vitritis was present.

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Photocin B and intravenous amphotocin 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 involve 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 amphotocin 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 (i.e., 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-
methotrim-sulfamethoxazole was prescribed. A 2-week course of outpatient intravenous therapy with ceftriaxone sodium was administered for the ocular infection. Six months after the onset of the condition, the results of a repeated magnetic resonance image scan of the brain disclosed resolution of the temporal lobe lesion. However, the patient’s visual acuity deteriorated to no light perception, the eye became phthisical, and it was enucleated 7 months after the onset of the ocular condition.

Histopathologic examination results of the vitreous specimens disclosed an intense polymorphonuclear leukocyte infiltrate. Light and electron microscopic evaluation of the retinal biopsy disclosed fibrinous material and a dense infiltrate of polymorphonuclear leukocytes and mononuclear inflammatory cells. No organisms were identified. Electron microscopic study of the subretinal biopsy disclosed numerous filamentous, septated organisms that measured 1.1 µm in diameter (Figure 3). 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 ciliochoroidal 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.

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 vitreotomy in nocardial endophthalmitis is uncertain. We injected amikacin and imipenem intravitreally in our patient. Although toxicity data are limited for imipenem,7,8 it displays comparable efficacy to intravitreal vancomycin in experimental Bacillus cereus endophthalmitis,9 and to amikacin in experimental Pseudomonas aeruginosa endophthalmitis.10 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 wherever 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.11 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 imipenem12 and other combinations.13,14

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

Supported in part by the FA Hadley Travelling Scholarship, the University of Western Australia, Perth, Australia, and the Independent Order of Odd Fellows, Winston-Salem, NC.

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


Figure 4. Filamentous organisms in the lung biopsy specimen (A and B, Gomori methenamine silver; original magnification ×1000).
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 McManis 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 neuroblasticomatous 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 to +5 mm of proptosis of that eye, and there was positive resistance to retropulsion. Pupils were 3 mm and sluggish bilaterally, without a relative afferent defect. The anterior chamber was quiet and of moderate depth. Biomicroscopy and funduscopic were unremarkable. Cycloplegic retinoscopy revealed a refraction of +3.50 +1.50 × 90 OD and +1.50 +130 × 90 OS. A magnetic resonance imaging scan showed a diffuse mass that enhanced with contrast in the left orbit. An orbital ultrasound revealed cystic cavities with fluid levels present within the orbit. Lymphangiogram was believed to be the most likely diagnosis, and the mass was observed.

By 6 months of age, the patient had progressive proptosis of her left eye. The extraocular movements remained intact, but the left eye was unable to fix. External examination of the left eye revealed a palpable mass in the inferolateral orbit. No relative afferent pupillary defect was present. Cycloplegic retinoscopy revealed increased hyperopia with a refraction of +4.00 +1.50 × 90 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. Note that the orbital rim is expanded and thinned without osseous destruction.

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 cleft-like structure lined partially by pseudostratified ciliated columnar epithelium and partially by keratinized stratified squamous epithelium. There were glandular 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 uniffer-
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 pa-tient. 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 question-able 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, OR 97201-4197 (e-mail: wilsonda@ohsu.edu).

4. Mayberger HW, Carlson AS, Lim S. Immature

**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 supplement 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 more 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 monocular 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-
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

This study was supported by an unrestricted grant from Research to Prevent Blindness Inc (New York, NY), and grants EY1252601 and EY10841-04 from the National Institutes of Health, Bethesda, Md.

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...
A Novel KRIT1/CCM1 Truncating Mutation in a Patient With Cerebral and Retinal Cavernous Angiomas

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 angiograms of the same eye showed a peripheral retinal vascular lesion, characteristic of a cavernous angioma (Figure 1A 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.
Comment. Retinal cavernomas are rare and usually asymptomatic. The largest series reported so far consists of 9 cases.2 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 KRI1.5 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 KRI1, 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 KRI1 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 KRI1 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

Dr Laberge-Le Couteulx received a fellowship from the Fondation pour la Recherche Médicale. Dr Labauge benefited from a poste d’accueil INSERM and was supported by the College des Enseignants de Neurologie. This work was supported by INSERM and the Ministère de l’Enseignement Supérieur et de la Recherche.

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 creatinine (<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, adrenocorticotrophic 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 electrooculogram 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 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.

Partial lipodystrophy with associated fundus abnormalities.

Exercise-Induced Vaso-spastic 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 ophthalmic artery, vasospasm, optic neuropathies, giant cell arteritis, angle-closure glaucoma, increased intracrural 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 pigmen
tary 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 antinuclear 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 and document the occlusion of 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).