Clinicopathologic Correlation of Idiopathic Polypoidal Choroidal Vasculopathy

Idiopathic polypoidal choroidal vasculopathy (IPCV), a peculiar hemorrhagic disorder of the macula involving serosanguineous detachments of the retinal pigment epithelium (RPE) and neurosensory retina, was first described by Yannuzzi1 at a meeting of the Macula Society in 1982. At the American Academy of Ophthalmology in 1984, Kleiner and coworkers2 described 7 patients with varying degrees of visual loss secondary to multiple recurrent hemorrhages or serous fluid beneath the RPE and neurosensory retina in the posterior fundus, and coined the phrase posterior uveal bleeding syndrome for this condition. In 1985, Stern and coworkers3 published the first report on “multiple recurrent serosanguineous RPE detachments” in 3 middle-aged black women. In his 1987 atlas, Gass4 described 3 black women with subretinal bleeding from multicentric neovascular networks with orange sub-RPE plaques or nodules in the peripapillary region.

Several additional reports and case series5-11 and 2 clinicopathologic studies12,13 have been published. The previously published pathologic reports as well as the current case may represent end-stage disease in IPCV. Herein, we describe and correlate the clinicopathologic findings in an enucleated eye with IPCV.

Report of a Case. A 46-year-old black woman was referred to one of us (J.L.D.) for evaluation of a mass in the left eye on November 20, 1995. Her medical history was significant for hypertension for 10 years and diabetes mellitus for 6 years (insulin-dependent for 3 years). The patient had smoked half a pack of ciga-

Figure 1. Montage fundus photograph of left eye (October 11, 1995) reveals peripapillary red-orange nodular lesions contiguous with elevated, sinuous, tubular lesions extending through the macular region. Note subretinal pigment epithelial hemorrhage superotemporal to the optic disc and the red-orange nodular or polypoidal lesions just posterior to the hemorrhage (arrow). Also note the serosanguineous retinal detachment and few hard exudates inferotemporally.

rettes per day for nearly 30 years. The patient’s only complaint was occasional burning in both eyes with otherwise normal vision. The best-corrected visual acuity was 20/25 OU. The visual fields were full to finger counting in both eyes. No afferent pupillary defect was found. The motility was full. Slitlamp examination results were unremarkable. The intraocular pressure was 21 mm Hg OU. Ophthalmoscopic examination results revealed multiple areas of retinal-choroidal elevation with red-orange sinuous and tubular patterns within the peripapillary and macular regions in the left eye (Figure 1). Superotemporal to the optic nerve head, a dark red hemorrhagic pigment epithelial detachment was found adjacent to a red-orange nodular or polypoidal lesion. Inferotemporally, a hemorrhagic retinal detachment appeared as an orange subretinal mass with focal hard exudate. The right fundus was unremarkable. A fluorescein angiogram disclosed mottled hypofluorescence and hyperfluorescence throughout the posterior pole in the early frames (Figure 2A) and blockage of fluorescein transmission in the region of the inferotemporal hemorrhagic retinal detachment and the superotemporal hemorrhagic RPE detachment. Mild early hyperfluorescence was present in the regions corresponding to the elevated red-orange sinuous and tubular lesions in the peripapillary and macular regions. Hyperfluorescent polypoidal lesions with minimal fluorescein leakage were at the posterior margins of the hemorrhagic detachments (Figure 2B). An indocyanine green (ICG) angiogram was recommended; however, the patient reported a reaction to iodine after a hysterosalpingogram in 1980 and was advised not to take iodine. The patient was diagnosed as having IPCV, and observation was recommended.

On August 5, 1996 (about 10 months after the initial examination), the patient had an acute loss of vision in the left eye. She had eaten “bad cream cheese” and subse-
quentely developed nausea and vomiting. She awoke the next morning with markedly decreased vision and pain in the left eye. The visual acuity was 20/20 OD and hand motions OS. The intraocular pressure was 17 mm Hg OU. Ophthalmoscopic examination results revealed extensive subretinal and sub-RPE hemorrhage in the central macula extending beyond the vascular arcades in the left eye (Figure 3). Surgical removal of the hemorrhage was considered but rejected because of the extensive sub-RPE hemorrhage.

On October 13, 1997 (about 2 years after the initial examination), the patient returned with marked pain and redness in the left eye for 1 week. The visual acuity was 20/25 OD and no light perception OS. The intraocular pressure was 45 mm Hg OS. Gonioscopy revealed 270° of angle closure without neovascularization and anterior displacement of the iris-lens diaphragm in the left eye. Results of slitlamp examination revealed marked conjunctival hyperemia, microcystic and stromal corneal edema, a shallow anterior chamber with rare cells, no ruberosis iridis, and a clear lens in the left eye. Ophthalmoscopic examination results revealed a hemorrhagic retinal detachment in the left eye. Echography showed dense opacities beneath hemorrhagic kissing choroidal vs retinal/RPE detachments and a posterior disciform lesion in the left eye. The patient underwent multiple procedures in the left eye, including anterior chamber paracentesis, diode laser cyclophotocoagulation, and retrobulbar alcohol injection. The pain could not be managed adequately, the intraocular pressure rose to 84 mm Hg OS, and the eye was enucleated, with placement of a hydroxyapatite orbital implant. On December 29, 1998, the visual acuity in the right eye was stable at 20/25+1, and no diabetic retinopathy or IPCV was found in the right eye.
Gross examination revealed a left eye of firm consistency measuring 23 × 23.5 × 21.5 mm, with 3 mm of attached optic nerve. The cornea was hazy and measured 11.5 × 11 mm in diameter. The pupil measured 6 mm in diameter. There were no transillumination defects. The optic nerve was sectioned close to the sclera. A horizontal cut was made and the superior cap was removed. On sectioning, the anterior chamber was flat, and there was anterior displacement of the iris-lens diaphragm by dense vitreous hemorrhage and a bulbar hemorrhagic retinal detachment (Figure 5). Focal areas of sub-RPE and suprachoroidal hemorrhage were found. The sclera was grossly unremarkable. The optic nerve head was not visualized.

Results of microscopic examination of 250 serial stepped sections revealed a cornea with intraepithelial edema. The Bowman layer, the stroma, and Descemet membrane were unremarkable. There was moderate attenuation of the endothelium. The iris and lens were displaced forward by extensive intraocular hemorrhage, with the iris lining the posterior surface of the cornea. The angle was closed. Hemorrhagic necrosis with rounding up of pigment and thickening of the basement membrane of the pigmented ciliary epithelium were seen in the region of the ciliary body. The lens was cataractous with cortical globule formation and posterior migration of the lens epithelium. Focal necrosis of the lens epithelium was present anteriorly. Sub-RPE and intra–Bruch membrane choroidal neovascularization (Figure 6A-D) were noted in the peripapillary region nasal and temporal to the optic nerve head. The RPE overlying the intra–Bruch membrane choroidal neovascularization was relatively intact with apparent focal vacuolation (Figure 6B-D). Thin-walled, cavernous vascular channels (Figure 6A-C) that originated from branches of the short posterior ciliary arteries through defects in Bruch membrane (Figure 6D and E) in the peripapillary region were found in the intra–Bruch choroidal neovascular membrane. Similar cavernous vascular channels without an apparent muscular layer were also in the peripapillary choroid (Figure 6C). The vessels closest to the optic nerve head exhibited a muscular layer of 1 to 3 cells thick (Figure 6F). Branches of the short posterior ciliary arteries focally abutted Bruch membrane in the peripapillary region (Figure 6E). A few nodular and calcified drusen were in the peripapillary region. Focal calcium deposition was in Bruch membrane, particularly in the peripapillary region. A disciform scar with marked subretinal fibrosis, focal RPE hyperplasia in a tubuloacinarian configuration, focal bone formation, and a few blood vessels (subretinal and sub-RPE choroidal neovascularization) were in the macular region and detached by hemorrhage (Figure 6G). There were extensive hemorrhagic retinal and bullous RPE detachments with hemorrhagic necrosis (Figure 6A and B). Focal aggregates of chronic inflammatory cells were found in the choroid, choroidal neovascular membrane, inferior oblique muscle, and episclera. There was focal arteriolar sclerosis within the retina and choroid. Longitudinal sections of the optic nerve disclosed a focal area of retrolaminar cavernous optic atrophy. Cross-sections of the optic nerve disclosed a focal area of hemorrhagic necrosis involving the superior or inferior nerve fiber bundles.

Comment. The phrase “idiopathic polypoidal choroidal vasculopathy” was first used by Yannuzzi. Other phrases used to describe this condition include “posterior uveal bleeding syndrome” and “multiple recurrent serosanguineous RPE detachments.” In 1990, Yannuzzi et al, Kleiner et al, and Perkovich et al each published 3 small case series of this condition. A total of 28 patients (8-11 patients in each study) were described by the above authors. Demographic features included women (96%), black patients (79%), age range of 40 to 79 years (mean age, 58 years), bilateral findings (68%), hypertension (43%), and diabetes mellitus (14%). Clinically, each of the patients had predominantly peripapillary orange-red polypoidal subretinal choroidal lesions that appeared to be nodular protrusions emanating from the choroid and that were associated with serosanguineous detachments of the RPE and neurosensory retina. Fluorescein angiography typically revealed early mottled hyperfluorescence, with late pooling of fluorescein and occasional late leakage in the region of the polypoidal lesions. The lesions appeared somewhat smaller angiographically than clinically.

The natural course of the disease involved chronic and recurrent hemorrhagic detachments of the RPE and retina, with retention of good vision in most eyes with or without treatment. Vitreous hemorrhage occurred in 12 patients (43%). Laser photocoagulation was associated with resolution of the serosanguineous detachments and stabilization or improvement in vision in 6 of 9 patients. The large disciform macular scars commonly seen in age-related macular degeneration (ARMD) were not characteristic of this condition. In addition, drusen and other vascular, proliferative, and inflammatory diseases of the eye were not typically seen in these patients.

Indocyanine green videoangiography has shown 2 basic choroidal vascular patterns in IPCV: (1) a branching network of variably sized vessels in the inner choroid (most often in the peripapillary region); and (2) vascular dilations at the border of the network of vessels. The vessels in the network do
Figure 6. A, Peripapillary intra-BM CNV (between arrowheads) composed of thin-walled cavernous vascular channels. Note subretinal hemorrhage (asterisk) (HE; ×40). B, Subretinal RPE (intra-BM ×10 is between arrowheads) cavernous vascular channels (asterisks) at the posterior margin of hemorrhagic RPE detachment. The upper arrowhead identifies the RPE and inner aspect of BM; the lower arrowhead identifies the outer aspect of BM (PAS; ×100). C, Higher-power view of intra-BM CNV (between arrowheads) with thin-walled cavernous vascular channels. The upper arrowhead identifies the RPE and inner aspect of BM; the lower arrowhead identifies the outer aspect of BM. Note the intact overlying RPE with apparent vacuolation and the cavernous vessel in the choroid (asterisk) (PAS; ×100). D, Intra-BM CNV with arteriole traversing defect (between arrows) in the peripapillary BM (PAS; ×400). E, Branches (asterisks) of a short posterior ciliary artery in juxtapapillary choroid extending to BM (PAS; ×250). F, Juxtapapillary intra-BM membrane arteriole (asterisk) with muscularis of 1-3 cell layers thick (PAS; ×250). G, Disciform macular scar (asterisk) with focal bone formation (arrow), RPE hyperplasia in a tubuloacinar configuration (arrowhead), and few blood vessels. Note the adjacent subretinal hemorrhage to the right of the disciform scar (HE; ×40).
not follow expected choroidal lobular patterns and generally appear more numerous than expected from the clinical examination results. Spaide and coworkers\textsuperscript{14} emphasized the fact that the hemorrhagic and serous elevation of the RPE and retina appear to arise from the edge of the polypoidal lesions. Ross and coworkers\textsuperscript{15} reported 2 elderly black women with IPCV, retinal arterial macroaneurysms, and hypertensive retinopathy and suggested that the pathophysiology of IPCV might be analogous to hypertensive changes in the choroidal and retinal vasculature.

In 1997, Yannuzzi and coworkers\textsuperscript{9} reported on the expanding clinical spectrum of IPCV and added 20 additional cases to the 45 cases previously reported in the literature. The average age at initial consultation was 60 years, with patients typically first seeking examination between ages 50 and 65 years. Idiopathic polypoidal choroidal vasculopathy was most commonly found in deeply pigmented (4.2 pigmented: 1 white) women (5 women: 1 man). Black persons and Asians seem to be at greatest risk for developing IPCV. However, among the Japanese, the condition is unilateral in 91% and hypertensive retinopathy and suggested that the pathophysiology of IPCV might be analogous to hypertensive changes in the choroidal and retinal vasculature.

Clinical observations reveal that the lesions in IPCV typically progress with conversion of the polypoidal nodules into enlarging tubular components (as seen in our patient) and associated serosanguineous RPE and retinal detachments. The RPE detachment eventually flattens and extends tangentially in the plane of the inner choroid.\textsuperscript{9} Subsequent variable RPE atrophy may ensue. Indocyanine green angiography generally discloses early choroidal vascular hyperfluorescence, with uniform washout in the later stages, except when the polypoidal lesions are actively leaking. The ICG characteristics typically observed in classic or occult choroidal neovascularization in ARMD are not seen in IPCV.\textsuperscript{9}

Two possibly related histopathologic studies have been published. MacCumber and coworkers\textsuperscript{12} described a 58-year-old white man with a medical history of insulin-dependent diabetes mellitus for 38 years, hypertension for 6 years, and high myopia (7-8 diopters), who developed bilateral, multiple recurrent hemorrhagic detachments of the sensory retina and RPE that eventually led to rubeosis and blindness in one eye. The peripapillary polypoidal choroidal nodules characteristic of IPCV were not apparent in the clinical photographs published by MacCumber et al.\textsuperscript{15} The visual acuity was hand motions to light perception for 3 years prior to enucleation. Histopathologic examination results revealed extensive fibrovascular proliferation in the subretinal space and within Bruch membrane, 23 choroidal blood vessels traversing defects in Bruch membrane, and marked lymphocytic infiltration of the choroid and fibrovascular tissue with both T and B cells. Based on the pathologic findings, the patient was treated with immunosuppressive therapy (prednisone and cyclophosphamide). The patient subsequently developed vitreous hemorrhage in the remaining eye and at least 2 new areas of serosanguineous RPE detachment, with a decrease in visual acuity to 20/200 during the ensuing 2 years despite immunosuppressive therapy. The intra–Bruch thin-walled cavernous vascular channels noted in the current case (Figure 6A-C) were not observed. The histopathologic findings might represent end-stage disciform scarring associated with IPCV, ARMD, or some other entity, such as multifocal choroiditis associated with progressive subretinal fibrosis\textsuperscript{17} or progressive subretinal fibrosis and uveitis syndrome.\textsuperscript{18} Spraul and coworkers\textsuperscript{13} described a 47-year-old black woman who had a sub-RPE hemorrhage in the right eye that was associated with a reddish-orange subretinal lesion in both eyes in the superotemporal peripapillary region. The patient subsequently developed extensive choroidal hemorrhage that led to enucleation of the right eye. Histopathologic examination results revealed fibrovascular membranes within Bruch membrane and between Bruch membrane and the RPE. Numerous breaks in Bruch membrane were observed. Focal serosanguineous detachment of the RPE and total detachment of the retina were revealed. The demographic and historical features as well as the findings of intra–Bruch membrane choroidal neovascularization (CNV), a disciform scar, and extensive serosanguineous retinal detachment described by Spraul and coworkers\textsuperscript{13} were very similar to the current case. The histopathologic findings might represent end-stage disciform scarring associated with IPCV. The one published photomicrograph shows apparent arteriolar sclerosis within the choroid but no large, thin-walled, cavernous vascular channels within Bruch membrane, as in the current case.

A histopathologic report of a lesion in a patient with known IPCV was recently published by Shiraga and coworkers.\textsuperscript{19} A subfoveal choroidal neovascular membrane developed 8 months after pars plana vitrectomy, tissue plasminogen activator, and sulfur hexafluoride (SF\textsubscript{6}) injection for a submacular hemorrhage associated with IPCV in a Japanese patient. The patient underwent repeated submacular surgery, and results of the histopathologic examination of the excised membrane disclosed fibrovascular tissue between the retina and RPE without the thin-walled cavernous vascular channels described in our patient.

Lafaut and colleagues\textsuperscript{20} reported the histopathologic findings of an excised choroidal neovascular membrane in a patient with ARMD whose ICG angiogram disclosed a polypoidal choroidal vascular pattern. Pathologic examination results revealed a thick sub-RPE intra–Bruch membrane fibrovascular membrane with diffuse drusen and dilated thin-walled vessels that appeared saccular on serial sections and were located just external to the RPE and diffuse drusen. In the published photomicrographs, no muscularis is apparent in the thin-walled vessels. In addition, the cavernous configuration of the vessels that was found in our case was not observed by Lafaut and colleagues.\textsuperscript{20}

The histopathologic findings in our case further clarify the natural history of IPCV. The flat orange-red vessels noted clinically in the
peripapillary region in IPCV appear to be branches of the short posterior ciliary arteries abutting or causing effacement of the RPE (Figure 6E and F). The peripapillary network of vessels observed on results of ICG angiography is derived from these branches of the posterior ciliary arteries. Iijima and coworkers reported the findings on optical coherence tomography in 2 Japanese patients with IPCV and showed anterior protrusion of an orange subretinal mass corresponding to a polypoidal structure noted on ICG angiography and contiguity between the orange mass (nodule) and hemorrhagic detachment of the RPE. The authors suggested that the RPE and Bruch membrane overlying the polypoidal structure might receive sustained compression from the underlying mass, leading to thinning and defects in the RPE and Bruch membrane. Age-related changes in Bruch membrane, particularly calcium deposition and drusen formation, in the peripapillary region (as found in the current case) may also contribute to defects or cause gaps in Bruch membrane. These defects or gaps in Bruch membrane may permit the proliferation of choroidal neovascularization, which is a common histopathologic finding in each of the reported pathologic studies of possible IPCV cases.

In the original descriptions of cases of IPCV, less than 50% of the total number of patients with IPCV were documented to have systemic hypertension. However, in a subsequent report and update by Perkovich and coworkers in a small case series, 8 (89%) of 9 patients had a history of hypertension. The 5-year cumulative incidence of CNV in the fellow eye of patients with definite hypertension and juxtafoveal or subfoveal CNV secondary to ARMD in the Macular Photocoagulation Study was approximately 50%—indicating a statistically significant systemic risk factor for CNV. Additionally, in the argon laser study and in the krypton laser study, approximately 60% and 55% of the patients, respectively, had definite hypertension. The prevalence of hypertension increases with age and is higher in African Americans compared with white Americans.

Histopathologic features of chronic hypertension were noted in the retina and choroid in the current case and in the case reported by Spraul and coworkers. The choroidal vascular tone is controlled by autonomic (sympathetic) input in contrast to the autoregulation of the retinal vasculature. Perhaps increased perfusion pressure secondary to hypertension within the arteriolar branches of the short posterior ciliary arteries and associated vascular shunts (arterial-arterial, arterial-venular, or venular-venular) stimulates the prolapse and protrusion of these vessels through defects or gaps in Bruch membrane in the peripapillary region. With persistently elevated arterial blood pressure, the branches of the short posterior ciliary arteries become dilated (cavernous) distally along the course of the vessels and internal to the defect or gap in Bruch membrane, leading to the development of the elevated peripapillary polypoidal lesions. The polypoidal and subsequent tubular lesions as described by Yannuzzi and coworkers correspond histopathologically to the large thin-walled cavernous vascular channels (Figure 6A-C) and accompanying choroidal neovascularization observed within Bruch membrane in the current case. In the early stages, the lack of significant fluorescein leakage and/or staining in IPCV may be due to the relatively intact RPE (Figure 6B-D) overlying the intra-Bruch membrane choroidal neovascularization and polypoidal lesions. Dilatation and attenuation of the blood vessel wall with accompanying disruption of the endothelium in the polypoidal lesions secondary to elevated arterial blood pressure may lead to the leakage noted on ICG angiography and to the serosanguineous detachments of the retina and RPE.

The true relationship between IPCV and hypertension is unknown, and other pathogenetic factors are possible. Perhaps the abnormal cavernous choroidal vessels represent congenital or acquired vascular anomalies or malformations or anatomic variation. The demographic distribution of the disease in patients typically older than 50 years, the possible association with hypertension, and the histologic finding of intra-Bruch membrane choroidal neovascularization might suggest that IPCV is a form or variant of ARMD. Occasional drusen and focal calcification within Bruch membrane, as observed in our case, are pathologic findings that have also been described in studies of eyes with ARMD.

In summary, the network of peripapillary vessels seen on fluorescein and ICG angiography in IPCV corresponds histopathologically to branches of the short posterior ciliary arteries. The elevated polypoidal and tubular choroidal lesions correspond to large thin-walled cavernous vascular channels and accompanying choroidal neovascularization within the Bruch membrane. Continuity between the ciliary arteries and the intra-Bruch membrane vascular channels may explain the potential catastrophic intraocular hemorrhage in IPCV. Hypertension in conjunction with age-related or degenerative changes in Bruch membrane may play a role in the development of IPCV. The predilection for deeply pigmented individuals is unexplained.


Rapidly Progressive T-Cell Lymphoma of the Conjunctiva

 Conjunctival lymphoma classically presents as a salmon-colored infiltrate that evolves slowly over months to years. It is nearly always of B-cell lineage. In an analysis of ocular adnexal lymphoid tumors, 29% were polyclonal, 68% were monoclonal B-cell proliferations, 2% were indeterminate, 1% were null cell, and 0% were monoclonal T-cell proliferations. We report an unusual case of a rapidly progressive conjunctival mass that was the first manifestation of systemic T-cell lymphoma.

Report of a Case. A 72-year-old African American woman developed swelling of her left caruncle that dramatically enlarged throughout 21 days, prompting ocular examination. Her visual acuity was 20/200 OD and counting fingers OS from cataracts bilaterally. There was a painless, pink, multinodular mass occupying 60% of the bulbar surface from the caruncle to the lateral conjunctiva, and covering half of the cornea (Figure). Computed tomography scans revealed preseptal soft tissue swelling without an orbital component. The patient preferred 14 days’ observation while receiving topical steroid/antibiotic medication, but the mass enlarged to affect 75% of the conjunctival surface, inducing lower eyelid ectropion. Diagnostic punch biopsy was performed.

Histopathological examination revealed a diffuse infiltrate of poorly cohesive medium to large cells, with moderate prominent nucleoli, and moderate, sometimes eccentric, cytoplasm. Many cells displayed folded or cleaved nuclei. Gomori centers were absent, and numerous mitotic figures were present. Immunohistochemical stains for leukocyte common antigen (CD45), CD3, CD20, and CD8 were positive, suggestive of a lymphoid neoplasm of T-cell origin. B-cell marker, L26 (CD20), was negative. The final diagnosis was peripheral T-cell lymphoma.

A thorough systemic examination revealed no systemic lymphoma or mycosis fungoides. The patient was treated with 3500 rad (35 Gy) of radiotherapy to the left conjunctiva with rapid regression of the lymphoma (Figure 1). During her last week of radiotherapy, she experienced dysphagia and a 2.72 kg weight loss. She was discovered to have an obstructive nasopharyngeal mass, and cervical, inguinal, and popliteal lymphadenopathy. On examination of the biopsy specimen, the nasopharyngeal mass proved to be T-cell lymphoma, and radiotherapy (1300 rad [13 Gy]) was de-
livered to the site, and there was improvement. Systemic chemotherapy, using cytoxan, vincristine, and adriamycin, was administered for 2 cycles. The patient maintained poor follow-up for 11 months, and she subsequently died of an unknown cause.

Comment. Lymphomas can be broadly classified into Hodgkin and non-Hodgkin types. Non-Hodgkin lymphomas are a diverse group and include monoclonal neoplasms of B-cell or T-cell lymphocytes. T-cell lymphomas are much less common than B-cell lymphomas and are particularly rare in the ocular region.1,2 Of the few reported cases of ophthalmic T-cell lymphomas, most involved the orbit or eyelid, and followed known systemic T-cell lymphoma.3,4 Rapid progression throughout days to weeks, and poor systemic prognosis was a common feature. Systemically, however, T-cell lymphoma can progress rapidly in aggressive subsets or it can progress slowly as in mycosis fungoides. Cook and associates reviewed 2155 patients at the Mayo Clinic with known cutaneous T-cell lymphoma, and found infiltration of the eyelid in 0.3%, and conjunctiva in 0.05%.4 Thus, ocular involvement with T-cell lymphoma is exceedingly rare.

Using a MEDLINE search, we found one other case of T-cell lymphoma that initially presented in the conjunctiva, similar to our case.3 The conjunctival tumor in that case also showed rapid progression. The patient was a 63-year-old woman who presented with bilateral limbal conjunctival thickening and chemosis for 20 days, and histopathologic study revealed T-cell lymphoma.5 Our patient also had a rapidly enlarging conjunctival mass that began as a caruncular thickening and extended in 21 days to involve 60% of the bulbar conjunctiva. Both patients were found subsequently to have systemic T-cell lymphoma, with involvement of maxillary sinus in their case, and nasopharynx in our case. Thus, systemic evaluation is particularly important in these cases. In summary, we present an unusual case of a rapidly progressive salmon-colored conjunctival tumor that proved to be the first sign of systemic T-cell lymphoma.

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Comment. Congenital mydriasis is a very rare abnormality that occurs in combination with a failure of accommodation. Herein we describe 2 patients in whom these ocular defects are associated with patent ductus arteriosus (PDA).

Report of Cases. Case 1. This 15-week-old infant was first seen by us 2 weeks after she had undergone surgery for a large PDA.3 Her parents had observed the dilated pupils since birth. The photographically measured diameter of the round pupils was 6.5 mm. They were not reactive to light, to an eyelid closure effort, or to the administration of up to a 1% concentration of pilocarpine eyedrops. Streak retinoscopy revealed a refraction of OD +3.0 dioptr sphere (D sph) and OS +2.5 D sph that remained uninfluenced by topical application of pilocarpine. Apart from the lack of accommodation and pupillary constriction, all ocular findings were normal. No other pupillary abnormalities were known in the family. The infant was given spectacles to wear for focusing at close distance. Within the following 2 years, a tortuosity of the retinal arteries with several loops near the optic disc became apparent. Having now observed the girl for 9 years, the tortuosity has increased while the pupils have not become smaller (diameter, OU 6.78 mm). They did not dilate after administration of up to a 5% concentration of phenylephrine eyedrops. The iris stroma is hypotrophic, without crypts. Diaphanoscopy of the iris did not reveal an absence of the posterior pigmented iris epithelium nor was there any abnormal finding in the sphincter zone. The axial bulbus length is now OD 19.77 mm and OS 20.03 mm. Meanwhile, the refraction of +7.75 D sph combined with −1.0 cylinder × 171° OD and +7.25 D sph combined with −1.5 cyl × 172° OS is corrected by multifocal glasses. The visual acuity is 0.8 OD and 1.0 OS. The mental development of the girl is normal. Her length and body weight are near the third percentile.

Case 2. This prematurely born infant (at 34 weeks gestation; weight, 1940 g) had been operated on for a large PDA at the age of 2 weeks. The diameter of her pupils was 7 mm without change either to light or to the administration of up to a 1% concentration of pilocarpine eyedrops. There was also no dilatation after administration of a 5% concentration of phenylephrine eyedrops (photographic measurements). The examination with a handheld slitlamp revealed a persisting pupillary membrane (a grid of filiform tissue originating in the midstroma and reaching across the pupil). The iris stroma was hypotrophic, without crypts. Diaphanoscopy showed some small defects of the pigment epithelial layer at the 8- to 9-o’clock position of the left iris.
periphery. The lens was in its regular position. Indirect binocular ophthalmoscopy showed poor pigmentation of the fundus and a slight tortuosity of the retinal arteries. Streak retinoscopy revealed a refraction of OD +3.0 D sph and OS +2.5 D sph that did not change after application of 1% pilocarpine eyedrops. There was no known family history of other pupillary abnormalities. We prescribed a spectacle correction focusing at arm's length and have kept the infant under observation.

Comment. The first 2 reported cases of bilateral congenital mydriasis occurred in monozygotic twins. More females than males are affected, typically bilaterally. Unilateral congenital mydriasis was described, once in a male patient with Waardenburg syndrome. In hereditary cases, an autosomal dominant mode of inheritance and an X-linked mode with nonviability of males were discussed.

The pathophysiologic correlate of congenital mydriasis and lack of accommodation is not unequivocal so far. A complete lack of cholinergic sensibility of the iris sphincter and the ciliary muscle can be discussed. If complete agenesis of the parasympathetically innervated muscles were the cause, diaphanoscopy of the iris should have revealed an absence of the iris sphincter muscle, but there was only peripheral spotty loss of the posterior pigmented iris epithelium in 1 eye of our patient 2. In case of (acquired) neurogenic origin, cholinergic supersensitivity should be expected, but all the reported cases of congenital mydriasis showed either no or only poor reaction to pilocarpine. In one patient, a 4% pilocarpine solution constricted the pupil a little and a 10% phenylephrine solution led to a rapid dilatation, suggesting the presence of an iris sphincter and dilator muscle. In our 2 cases an (congenital) aplasia of the small cells of the oculomotor complex is imaginable, leading to an “orthograde transsynaptic dysgenesis” of the corresponding muscles (the same mechanism can be imagined if a lack of sensibility of the cholinergic receptors was the cause), thus also explaining the lack of a response to pilocarpine. The lack of response to phenylephrine might be explained by fibrosis of the sphincter muscle tissue. Alternatively, a dysgenesis involving all the intraocular muscles can be discussed. Ataxia and oligophrenia are excluded in our case 1, and so far case 2 also reveals no findings pointing to Gillespie syndrome.

An involvement of the ciliary muscle was recently mentioned in a case of congenital mydriasis. In most patients whose cases are reported in the literature, it cannot be excluded because of their old age. The history of one woman whose presbyopic symptoms had not appeared until she was 45 years old is only anecdotal. Regarding visual function, mydriasis may cause some glare and contribute to the blur of the retinal image, but the lack of accommodation is the decisive defect. To prevent amblyopia, correction of the refractive error is indicated with focusing at arm’s length (if accommodation is impossible) in infancy, and from 6 months onward with the use of bifocal glasses focusing at arm’s length and 1 m, and later with multifocal glasses. In addition, sunglasses are sensible.

Congenital mydriasis is an extremely rare condition, and the incidence of extreme PDA is low. Of 15 reports—several of which are based only on history and are not thorough—there are 3 well-documented cases that bear testimony to an association between bilateral congenital mydriasis, insufficiency of accommodation, and PDA. Such an association can therefore hardly be explained by pure chance. As a fundamental pathophysiologic mechanism, a receptor defect of the smooth muscles of both the eye and the media of the ductus arteriosus can be hypothesized. Further investigation will be necessary to elucidate the frequency and the mechanism of the link between a large PDA and a congenital defect of the ciliary muscle and the iris sphincter as well as the tortuosity of the retinal vessels. Any patient with a PDA should undergo a careful examination of the function of the intraocular muscles.

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Cytomegalovirus Retinitis in Patients With Good Syndrome

Hypogammaglobulinemia and secondary systemic opportunistic infections are recognized associations in patients with thymoma, and the simultaneous occurrence of thymoma and hypogammaglobulinemia is referred to as Good syndrome.

We report herein the presentation, clinical course, and outcome of 2 consecutive patients with vitreous biopsy–proved cytomegalovirus (CMV) retinitis associated with thymoma and immunodeficiency but with no evidence of other systemic CMV infection.

Report of Cases. Case 1. A 45-year-old woman was referred to Moorfields Eye Hospital, London, England, in November 1998 with a 2-month history of bilateral posterior uveitis that was not responding to topical treatment. The patient had no history of ocular disease, and her medical history included a thymoma treated by excision and postoperative radiotherapy in 1996, myasthenia gravis (positive acetylcholine receptor antibody), vasculitis (p-anti-neutrophil cytoplasmic antibody positive) with mild
The patient had no serum antibod-
ies for human immunodeficiency vi-
ruses 1 and 2 and had markedly low IgA levels (44 mg/dL), with mildly elevated IgM (199 mg/dL) and IgG (2020 mg/dL) levels. Polymerase chain reaction examination of peripheral blood was negative for CMV DNA. The patient’s CD4 cell count did not return to normal, and her immune status remained unchanged despite cessation of azathioprine therapy. A chest x-ray film was clear, with no evidence of opportunistic infection. Because her retinitis was improving after a week of systemic treatment, the patient was discharged from the hospital on a regimen of oral acyclovir (because the patient preferred not to receive ganciclovir) and a tapering course of oral prednisolone. Six weeks later, the retinitis relapsed in the left eye and treatment was changed to intravenous ganciclovir followed by insertion of a slow-release intravitreal implant. The retinitis in her left eye resolved after 1 week, and the ganciclovir implant has been subsequently exchanged on a regular basis to control the patient’s disease because her CD4 cell count has remained low.

Case 2. A 65-year-old woman was referred to Moorfields Eye Hospital in April 2000 with a 1-week history of floaters and progressive reduction in visual acuity of the right eye after a flu-like illness that lasted a few days. The patient had no history of ocular disease, but her medical history was remarkable for a malignant thymoma that had been excised in 1998 and recurrent chest infections associated with bronchiectasis. On examination, her visual acuities were hand movements and 20/20 OS, with a right-sided relative afferent pupillary defect. Slitlamp examination showed a mild right anterior uveitis with normal intraocular pressures. Funduscopic examination showed a moderate vitritis and a swollen, hyperemic optic disc associated with retinitis along the right inferotemporal vascular arcade and affecting the macula (Figure 2). Polymerase chain reaction examination of a vitreous tap confirmed the presence of CMV DNA and was negative for herpes simplex viruses 1 and 2, herpes zoster virus, and Epstein-Barr virus DNA. The patient was treated with topical corticosteroids and repeated intravitreal injections of foscarnet sodium (2.4 mg each) and oral gancyclovir (1 g 3 times daily). Despite control of the retinitis, the patient’s vision failed to improve because of optic atrophy. Polymerase chain reaction examination of peripheral blood was negative for CMV DNA. A chest x-ray film was not suggestive of any acute opportunistic infections, and analysis of blood samples showed a raised CD8 cell count of 976 cells/µL (reference range, 200-900 cells/µL), with a reduced CD4/CD8 ratio of 0.6 (reference range, 0.66-3.52) and a low B lymphocyte count of 1 (reference range, 100-500). The patient had no serum antibodies for human immunodeficiency viruses 1 and 2, low IgA (56 mg/dL) and IgM (43 mg/dL) levels, and a normal IgG level (640 mg/dL).

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Clinicians should be aware of this association, as early recognition and treatment can improve prognosis.

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Unilateral, Idiopathic Leopard-Spot Lesion of the Retinal Pigment Epithelium

Several conditions have been described as having a leopard retinal spot pattern.1-6 We report a similar pattern, observed in 1 eye each of 4 young patients (Figure 1), and discuss how this condition is distinct from previously described lesions; in 2 cases, these leopard-spot lesions were associated with choroidal neovascularization (CNV).

Report of Cases. Case 1. A 34-year-old man was seen because of metamorphopsia. Visual acuity was 20/20 OU. Medical history and slitlamp examination findings were unremarkable. Findings from right fundus examination were normal. Left fundus examination disclosed a round lesion that was located at the level of the retinal pigment epithelium (RPE) in the posterior pole (Figure 1A) above the macula and a localized serous retinal detachment. Fluorescein angiography showed CNV at the inferior border of the lesion. Krypton laser photocoagulation was applied to the new vessel. Three weeks later an additional angiogram was performed (Figure 2A), which was of better quality than the initial study. This study showed a leopard-spot pattern at the periphery of the lesion, with hypofluorescent dots surrounded by reticular staining with the dye. The photocoagulation scar appeared dark. B-scan ultrasonography did not show any signs of calcification within the lesion. The lesion appeared to remain stable during a 2-year follow-up.

Case 2. A 27-year-old man consulted us because he needed an attestation to renew his boxing license. Visual acuity was 20/25 OD and 20/20 OS. Medical history and slitlamp examination findings were unremarkable. Results of left fundus examination were within normal limits. Right fundus examination, however, disclosed a deep, large, greyish lesion in the interparapapillary area, with a leopard-spot pattern at its periphery (Figure 1B). A tiny epiretinal membrane was observed at the inferonasal aspect of the macula, which was associated with 2 small hemorrhages. The leopard-spot pattern appeared more obvious on fluorescein angiography (Figure 2B). Fluorescein angiography also disclosed tortuosity and kinking of arterioles and venules located nasally and inferiorly to the macula. We interpreted these anomalies of the retinal vessels as a consequence of the epiretinal membrane. B-scan ultrasonography did not show any signs of calcification within the lesion. Unfortunately, the patient was lost to follow-up.

Case 3. A 16-year-old girl was seen with a complaint of “visual fatigue.” Visual acuity was 20/20 OD with correction (+0.50 OD, 90° +0.25 OS). Medical history and slit-
lamp examination findings were unremarkable. The left fundus appeared normal. Right fundus examination disclosed an irregular lesion located at the level of the RPE, in the papillomacular area, with dark dots surrounded by a whitish reticular net (Figure 1C). The leopard-spot pattern appeared more obvious on fluorescein angiography (Figure 2C). Follow-up was limited to 6 months, but there was no change during this time.

**Case 4.** A 24-year-old man was seen for visual loss and metamorphopsia of the right eye. Visual acuity was 20/128 OD and 20/20 OS. Medical history revealed type 2 diabetes mellitus, which was diagnosed when the patient was 2 years old and treated solely by diet. His mother also had type 2 diabetes mellitus. Slitlamp examination findings were unremarkable. The left fundus appeared normal, but the right fundus showed a deep, oval macular lesion with a whitish reticular border. A central macular detachment was also observed (Figure 1D). Fluorescein angiography showed a leopard-spot-patterned lesion associated with a juxtafoveal CNV (Figure 2D). A feeder vessel was observed in the early frames with leakage of dye on late frames (Figure 3A-B). Indocyanine green angiography also showed the CNV on early frames and a hypofluorescent lesion on late frames (Figure 3C-D). The reticular peripheral net that was hyperfluorescent on fluorescein angiography appeared hypofluorescent on indocyanine green angiography. B-scan ultrasonography did not reveal any signs of choroidal calcification. The CNV was then treated with krypton laser photocoagulation. To date (6-month follow-up), no recurrence has occurred. A previous ophthalmic examination had been performed 10 years ago because of the patient’s diabetes. The medical report at that time described a visual acuity of 20/20 OU, pigmented alterations of the right fundus, but no suggestion of diabetic retinopathy. An angiogram had also been performed (Figure 3E). Comparison of previous and recent angiographies disclosed marked progression of the leopard-spot lesion.

**Comment.** Herein, we have described 4 young patients, 3 men and 1 girl, who presented with a round lesion of one posterior pole. The lesion had a leopard-spot pattern observed on color fundus photographs and, more obviously, with fluorescein angiography. B-scan ultrasonography, performed in 3 cases, did not

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**Figure 1.** Fundus photograph of the posterior pole of cases 1 (A), 2 (B), 3 (C), and 4 (D). Round lesions with peripheral dark dots result in a leopard-spot pattern. The lesions are located at the level of the retinal pigment epithelium (RPE) and include fibrosis, hyperplastic changes of the RPE at the periphery, and thinning and atrophy of the RPE at the center.
reveal any calcification. Choroidal neovascularization was observed in 2 patients, in one case at the border of the lesion and in one case within the leopard-spot lesion.

Several systemic conditions may be associated with a leopard-spot pattern of the fundus, including leukemia, systemic form of large-cell non-Hodgkin lymphoma, systemic carcinoma with bilateral diffuse uveal melanocytic proliferation, and idiopathic uveal effusion syndrome. However, all of these acute conditions appear differently from the asymptomatic pattern observed in our patients, whose troubles were confined to a localized part of the retina, without associated systemic or ocular conditions.

Patients with chronic idiopathic central serous chorioretinopathy may have a bone corpuscular pattern of migration of pigment in areas of recurrent and/or chronic serous detachment. This pattern is more frequently observed in patients receiving high doses of corticosteroids. None of our patients had previous episodes consistent with typical chronic idiopathic central serous chorioretinopathy, and none received corticosteroids. Furthermore, chronic idiopathic central serous chorioretinopathy is unlikely to develop in a 16-year-old girl (case 3).

Trauma should be taken seriously as a possible cause of the pattern observed in the present cases. Traumatic choroidopathy can result from acute contusion necrosis of the RPE. Rupture in the inner choroid and RPE may be absent, but hemorrhagic detachment of the retina is frequently observed. Resolution of the detachment and hemorrhages may then reveal varying degrees of RPE atrophy. Case 2 acknowledged many instances of trauma to the face during his boxing activities. However, none of the 4 patients remembered severe ocular trauma. Moreover, a traumatic origin appeared particularly unlikely in case 4, for whom comparison of recent and previous angiograms showed marked changes (Figure 3). In this case, one could assume that secondary hyperplastic changes followed initial sequelae of trauma; however, a lack of recollection of severe trauma in all patients and demonstration of evolution of the lesions in one case led us to hypothesize that a traumatic cause is unlikely. However, ocular trauma cannot be ruled out because it could have occurred during infancy or childhood without any recollection.

Choroidal or subretinal neovascularization is an acquired abnormality observed in many congenital, degenerative, infectious, inflammatory, tumoral, and traumatic processes, some of which are more commonly observed in young patients. Among these conditions,
choroidal osteomas may show a pattern similar to that seen in our patients. Choroidal osteomas, in summary, are unique, unilateral tumors that arise in the juxtapapillary and macular region of young adults. They typically have an orange hue but may show some mottling of gray pigment on the surface. The osteoblastic activity of osteomas may encapsulate some osteoclastic change. Feeder vessels may be observed exiting from the holes in the anterior surface of the cancellous bone. This process can evolve to true choroidal neovascular membranes, which may reveal the osteoma. Case 4 also developed CNV with a typical feeder vessel. However, marked attenuation of sound by the tumor ultrasonographically, which is typical of choroidal osteomas, could not be demonstrated in our study in the 3 patients so tested. In our cases, RPE
changes may have facilitated the occurrence of CNV.

In summary, to our knowledge, the peculiar leopard-spot pattern of the retinal lesion observed in our 4 patients has not been previously reported. Because the cause of these lesions remains unclear, we have designated them as unilateral, idiopathic leopard-spot lesions of the RPE. Lack of histologic analysis precludes more discussion on the possible etiologic nature of the disorder, which seems to associate fibrosis and hyperplastic changes of the RPE at the periphery of the lesion and thinning and atrophy of the RPE at the center.

However, we could not rule out trauma as a possible cause of these lesions, and they may also represent a similar end stage of different causes. The condition is probably very rare, and its prognosis likely depends on whether CNV develops, which was observed in 2 of our 4 patients.

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Retinal Venous Occlusion as the Initial Sign of Tetralogy of Fallot

Tetralogy of Fallot was originally described in 1888.1 It is primarily encountered in the pediatric population. It was described by Etienne-Louis A. Fallot to consist of pulmonary atresia, dextroposed aorta, interventricular septal defect, and right ventricular hypertrophy. Approximately 3% of patients survive to age 40 years without surgical intervention.2 Longevity is believed to correlate with greater pulmonary flow and milder degrees of arterial desaturation. Herein, we describe a patient whose cardiac abnormality had gone undetected for 50 years until he came to the eye clinic with visual complaints.

Report of a Case. A 50-year-old Caribean man came to the ophthalmology clinic complaining of a 5-month history of blurred vision in the right eye. He stated that he saw an ophthalmologist 5 months earlier when the symptoms started but failed to return for follow-up owing to financial constraints. Ten days prior to this visit, the patient reported having similar episodes of blurred vision in the left eye. His visual acuity was 20/25 OD and 20/30 OS. The pupils, extraocular muscles, intraocular pressure readings, and findings of external and slitlamp examinations were unremarkable. Dilated fundus examination revealed superficial hemorrhages in the inferiortemporal quadrant of the retina in the right eye associated with vessel tortuosity. Disc edema associated with diffuse retinal hemorrhages and dilated tortuous veins was seen in the left eye. These findings were consistent with a branch retinal vein occlusion in the right eye and a central retinal vein occlusion (CRVO) in the left eye.

A workup was initiated and included complete blood cell count, erythrocyte sedimentation rate, blood pressure evaluation, levels of fasting blood glucose and glycosylated hemoglobin, prothrombin time, partial thromboplastin time, fluorescent treponemal antibody level, VDRL, antichordiolipin antibody level, and a carotid ultrasound.

The blood test results were significant for a hemoglobin level of 19.4 g/dL and a hematocrit of 59.4%. The patient was referred to the hematologic department for evaluation of polycythemia. Subsequently, he was found to have decreased oxygen saturation by arterial blood gas analysis and a cardiac murmur. An increased level of erythropoietin was found, raising the suspicion that the polycythemia was due to an underlying condition causing hypoxemia. On further evaluation, a transesophageal echocardiogram revealed the classic tetrad of pulmonic stenosis, ventricular septal defect, dilated overriding aorta, and severe right ventricular hypertrophy with a right to left shunt, consistent with tetralogy of Fallot.

The patient had never experienced any symptoms of congenital heart disease despite his very active life as a merchant marine; at the time of initial examination, the patient worked as a construction supervisor. On questioning, he reported the recent onset of exertional dyspnea, which limited his exercise tolerance to 3 or 4 city blocks of walking. A cardiac catherization was performed and the patient ultimately underwent surgical repair of his congenital cardiac defect. The retinal hemorrhages resolved, the vision remained stable, and the patient continues to receive regular follow-up.

Comment. A CRVO is often a result of a combination of local and systemic factors. The mechanisms that produce the clinical picture of a CRVO can be divided into (1) conditions that produce a physiologic blockage at the level of the lamina cribrosa and (2) conditions in which hemodynamic factors result in an obstruction to the blood flow. A combination of these mechanisms may occur in a patient with a CRVO. Likely causes include atherosclerosis of the adjacent central retinal artery (causing compression of the vein in the lamina cribrosa region and inducing thrombosis in the lumen of the vein), hypertension, optic disc edema, glaucoma, optic disc drusen, elevated homocysteine levels,

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hypercoagulation states (eg, lymphoma, leukemia, antiphospholipid syndrome, activated protein C resistance, and polycythemia), vasculitis (eg, sarcoid, syphilis, systemic lupus erythematosus), drugs (eg, oral contraceptives, diuretics), retrobulbar external compression (eg, thyroid, orbital tumor), and rare causes, such as migraine.

An appropriate workup for a young person who is found to have venous occlusion on initial examination includes blood pressure readings, fasting blood glucose level, glycosylated hemoglobin level, complete blood cell count with differential cell count, platelet count, serum protein electrophoresis, lipid profile, and rapid plasma reagin/fluorescent treponemal antibody absorption test. If clinically indicated, this basic workup can be extended to include antinuclear antibody levels, hemoglobin electrophoresis, cryoglobulins, antiphospholipid antibody levels, and a chest radiograph. A complete medical evaluation with attention to the possibility of cardiovascular disease is necessary; the complete workup is best done in conjunction with an internist. Frequent ophthalmic examinations are to be performed thereafter.

Although our patient had been asymptomatic for many years, he had recently developed symptoms caused by his cardiac anomaly. As a result, the decision was made to perform surgical repair before any further cardiac deterioration could ensue.

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