Polypoidal Choroidal Vasculopathy and Neovascularized Age-related Macular Degeneration

Lawrence A. Yannuzzi, MD; Doric W. K. Wong, MD; Baldo Scassellati Sforzolini, MD; Mauro Goldbaum, MD; Kong C. Tang, MD; Richard F. Spaide, MD; K. Bailey Freund, MD; Jason S. Slakter, MD; David R. Guyer, MD; John A. Sorenson, MD; Yale Fisher, MD; David Maberley, MD; Dennis A. Orlock, CRA

Objective: To determine the nature and frequency of polypoidal choroidal vasculopathy (PCV) in a series of patients suspected of having neovascularized age-related macular degeneration (AMD).

Methods: A prospective analysis of 167 consecutive, newly diagnosed patients aged 55 years or older with presumed neovascularized AMD was performed. All patients were examined with fundus biomicroscopy as well as fluorescein and indocyanine green angiography.

Results: Choroidal neovascularization secondary to AMD was diagnosed in 154 (92.2%) of 167 patients; 13 (7.8%) patients had PCV. The patients affected by PCV were younger than those with AMD (P = .01). Peripapillary choroidal neovascularization was seen in 3 (1.9%) of 154 patients with AMD and 3 (23.1%) of 13 patients with PCV (P = .006). Significant drusen were present in 63 (70%) of 90 fellow eyes with unilateral AMD compared with only 1 (16.7%) of 6 eyes with PCV (P = .02). Only 5 patients with AMD (3.2%) were nonwhite compared with 3 patients with PCV (23.1%) (P = .02).

Conclusions: A measurable number of elderly patients with findings suggestive of neovascularized AMD and serosanguineous macular manifestations will instead have PCV. Polypoidal choroidal vasculopathy can occur in any sex or race, but is more commonly seen in the peripapillary area, without associated drusen, and in nonwhite patients. It is important to differentiate AMD from PCV because there are significant differences in the demographic risk profile, natural course, visual prognosis, and management of these patients.


For nearly 2 decades, ophthalmologists have been aware of a peculiar hemorrhagic disorder of the macula, called idiopathic polypoidal choroidal vasculopathy (IPCV).1-9 It was originally described as an inner choroidal vascular abnormality with 2 distinct components: (1) a network of branching vessels external to the choriocapillaris, and (2) terminal aneurysmal dilations sometimes seen clinically as reddish-orange, spheroidal, polyplike structures or polypoidal vascular lesions (Figure 1). Patients with this disorder are known to be at risk of experiencing large serous and hemorrhagic detachments of the retinal pigment epithelium (RPE) and the neurosensory retina (Figure 2, A). Idiopathic polypoidal choroidal vasculopathy is typically described as a bilateral, peripapillary disorder of middle-aged black women (Figure 2, B). If the polypoidal lesions are large enough, and there is sufficient atrophy of the overlying RPE, they may sometimes be detectable clinically or with fluorescein angiography; however, they are best identified with indocyanine green (ICG) angiography, which can more clearly image the choroid through the RPE and the secondary serosanguineous complications.8,9 It is generally accepted that ICG angiography is the diagnostic adjunct of choice in identifying the vascular components of the IPCV abnormality with increased sensitivity and specificity.7 Recently, Yannuzzi et al,9 in an update on the clinical spectrum of IPCV, reported that choroidal vasculopathy may also occur as an isolated entity in the macula in individuals of all races and sexes with a broad age range and a marked variability in the morphology and natural course of the abnormal vessels (Figure 3). Also in this report, it was concluded that the pathogenesis of the vascular abnormality in IPCV was most likely a variant of choroidal neovascularization (CNV) with a separate or independent set of demographic risk factors, clinical features, angiographic characteristics, natural course, and visual prognosis. Numerous other reports have subsequently confirmed and expanded on...
PATIENTS AND METHODS

A consecutive series of 167 newly diagnosed, elderly, symptomatic patients (age ≥55 years) with an exudative maculopathy and the presumed diagnosis of neovascularized AMD were studied prospectively. In all cases the clinical diagnosis had been made within 3 months from the onset of their visual symptoms. Eligible patients required serous and/or hemorrhagic detachments of the macula. The patients were mostly referred to the private retinal specialty offices of the authors (151 cases) or to the retinal service of the affiliated institution, the LuEsther T. Mertz Retinal Research Center of the Manhattan Eye, Ear and Throat Hospital, New York, NY (16 cases) during a period of 4 months, from October 1998 through January 1999. Each patient had a complete ocular history, slitlamp examination, and posterior fundus examination, including slitlamp biomicroscopy with a Goldmann contact lens and indirect ophthalmoscopy. All patients also had an intravenous fluorescein angiogram with 5 mL of 10% sodium fluorescein and an ICG angiogram with a 25-µg total dose with informed consent. Only the eye with acute visual symptoms was entered in the study. Whenever a patient had an adequate hard-copy fluorescein angiogram from a referring physician, it was used. The angiograms were read by a committee (D.W.K.W., B.S.S., K.C.T., R.F.S., and K.B.F.). If there were uncertainties in interpretation, the decision was referred to the lead author (L.A.Y.).

Patients were excluded if they had other forms of neovascularized maculopathy, such as pathological myopia, angioid streaks, trauma, inflammation, the presumed ocular histoplasmosis syndrome, and multifocal chorioiditis. Previously known sensitivities to the fluorescein or ICG dye were also considered to be ineligibility factors, but no such patient was excluded for this reason in the series.

These observations, clearly establishing the existence of a geographically widespread condition.10-20

A more recent term, polypoidal choroidal vasculopathy (PCV), has been proposed to describe this entity with the assumption that it represents a distinct form of CNV, specifically termed polypoidal CNV. The use of this term has been recently supported by a few clinical histopathological studies that show large, thin-walled, choroidal vessels beneath the RPE, predominantly external to the choriocapillaris with choroidal capillary proliferation.14-16

Within the expanded clinical spectrum of PCV, there is a likely possibility that some patients initially classified as having neovascularized age-related macular degeneration (AMD) may actually have exudative and/or hemorrhagic macular manifestations secondary to polypoidal CNV rather than the characteristic, small capillary proliferation into Bruch’s membrane or more typical CNV. Because of known differences in the natural course, visual prognosis, and potential response to treatment, it would be clinically desirable to differentiate PCV from neovascularized AMD. The purpose of this study was to determine in a prospective, consecutive series of elderly patients with exudative maculopathy both the nature and frequency of PCV, as well as the clinical differences between patients with PCV and those with neovascularized AMD.

DEFINITIONS USED IN THE STUDY

The following standards and definitions were used to describe the related clinical and angiographic abnormalities employed in the series: (1) Exudative maculopathy: a serous and/or hemorrhagic detachment of the macula noted on clinical slitlamp biomicroscopic examination. (2) Classic CNV: early lacy hyperfluorescence with well-demarcated margins and late leakage on fluorescein angiography. (3) Occult CNV: areas of leakage in the late phase of the angiogram not corresponding to a classic CNV discernable in the early phase of the angiogram. Early vascular hyperfluorescence and late subretinal staining are usually evident on ICG angiography. (4) Polypoidal CNV: Branching inner choroidal vessels external to the choriocapillaris with terminal dilations that demonstrate early, intense, local or multifocal hyperfluorescence corresponding to the aneurysmal or polypoidal lesions imaged with ICG angiography (Figure 1). (5) Active polypoidal CNV: Early intense hyperfluorescence and late leakage or staining of the polypoidal lesion (Figure 4). (6) Inactive polypoidal CNV: Gradual fading or “wash-out” of the polypoidal lesion in the late stages of the study (30-40 minutes after injection of the dye (Figure 4). (7) Significant drusen: At least 5 large drusen (>63 µm). (8) Significant serous pigment epithelial detachment (PED): Larger than 2 disc areas.

STATISTICAL ANALYSIS

The 2-tailed Fisher exact test, χ² test, and t test were used for data analysis.

RESULTS

One hundred sixty-seven patients were enrolled in this study. There were 67 men and 100 women; the subjects’ ages ranged from 55 to 96 years with a mean age of 74.4 years. One hundred fifty-four (92.2%) were diagnosed with neovascularized AMD; the remaining 13 patients (7.8%) were diagnosed with PCV. Subjects with PCV (mean age, 73.26 years; SD, 8.98 years) were significantly younger than those with AMD (mean age, 78.94 years; SD, 7.63 years) (P = .01). In 3 (23.1%) of 13 patients with PCV the CNV was peripapillary, whereas in only 3 (1.9%) of 154 patients with AMD was the CNV found in the peripapillary area (P = .006). Ninety (58.4%) of 154 patients with AMD had evidence of unilateral exudative disease compared with 6 (46.2%) of 13 PCV cases (P = .38). Significant soft drusen (diameter >63 µm) were observed in the fellow eyes of 63 (70%) of 90 patients with unilateral disease in the AMD group and in 1 (16.7%) of 6 patients with unilateral disease in the PCV group (P = .02). A large serous PED (>2 disc areas) was seen in 16 (10.4%) of 154 pa-
tients with AMD and in 3 (23.1%) of 13 patients with PCV. No statistically significant difference regarding the frequency of such PEDs was seen between the 2 groups ($P = .17$).

Only 5 (3.2%) of the 154 patients with AMD were nonwhite (0 blacks, 3 Hispanics, 2 Asians), compared with 3 (23.1%) of 13 patients with PCV (2 blacks, 1 Hispanic, 0 Asians) ($P = .02$). Ninety-four (61%) of 154 patients with AMD and 6 (46.2%) of 13 patients with PCV were female. No difference in sex prevalence was found between the 2 groups of patients ($P = .45$).

**COMMENT**

Polypoidal choroidal vasculopathy has been considered to be a distinct clinical entity involving the choroidal circulation. The vascular abnormality lies in the inner choroid, external to the choriocapillaris, consisting of 2 fundamental elements: a dilated network of vessels and multiple terminal aneurysmal protuberances in a polypoidal configuration (see figures).5,9,16,17 These polypoidal lesions appear to account for the episodic leakage and bleeding under the RPE and neurosensory retina that can
occur in these patients. In some cases the exudative changes can lead to variably sized serosanguineous PEDs (Figure 2, B). Some patients may also experience bullous retinal detachment and vitreous hemorrhage. With disturbance of the subretinal anatomical architecture from leakage and bleeding, or merely from the proliferation of the polypoidal vascular abnormality, more typical CNV (classic or occult) may evolve with proliferation of small-caliber vessels in the region of the choriocapillaris and into the remaining portions of Bruch’s membrane. In our experience some patients with PCV may even develop classic CNV without antecedent serosanguineous detachment.

Following the report by Yannuzzi et al on the expanded clinical spectrum of PCV, we have noted polypoidal CNV-type vessels after the therapeutic irradiation of neovascularized AMD. A patient with angioid streaks and several patients with idiopathic CNV have also been identified as having neovascularization of the polypoidal CNV type. Furthermore, polypoidal CNV has been reported to occur in the peripheral fundus as a singular entity. Since that report we have seen other cases of polypoidal CNV involving the peripheral retina in a bilateral, multifocal distribution. One such eye also experienced an explosive choroidal hemorrhage during an uncomplicated cataract operation. It was this increasing awareness and recognition of this form of CNV in a broader range of patients with hemorrhagic manifestations in the fundus that encouraged us to study this current series of patients with presumed neovascularized AMD for the presence of PCV.

A frequency of 7.8% for PCV in this series was not unexpected for our urban center, which has a mixed racial population. Polypoidal choroidal vasculopathy is...
known to have a predilection for more darkly pig-
mented individuals; however, most of the cases of PCV
in this series were in white patients. Another expected
result was the lower incidence of significant drusen in
the fellow eye of patients with PCV, compared with
their counterparts with AMD, who had unilateral macu-
lopathy.

As with previous reports, this study also demon-
strated greater likelihood for polypoidal CNV to be in the
peripapillary area, when compared with AMD. When race
was defined as nonwhite (including blacks, Hispanics,
and Asians), PCV was more common in the nonwhite
population. In contrast, very few patients in the neovas-
cularized AMD group were nonwhite, and not a single
one was black. This reinforces the well-known observa-
tion that neovascularized AMD is rarely encountered in
black patients.

Unexpected results in this series are the lack of a
female sex predilection and the involvement of white pa-
tients in the polypoidal CNV subgroup. Polypoidal vas-
culopathy was originally described predominantly in black
women. Curiously, in Japan polypoidal CNV is evident-
ially more prevalent in men. Men with PCV were
as common as women in this series. In contrast, there is
a well-known tendency for women to be at risk for neo-
vascularized AMD in our country.

Another unexpected finding was the presence of
large, serous detachments of the RPE in patients with pol-
ypoidal CNV. While the number of patients involved was
too small to show statistical significance as compared with
neovascularized AMD, a large serous PED was more fre-
cently found in patients with PCV (Figure 3, B). It is
of interest in that only certain exudative disorders of the
macula are commonly associated with serous or hemor-
hagic PEDs. These include central serous chorioret-
nopathy, AMD, and PCV. In other neovascularized macu-
lopathies, such as the presumed ocular histoplasmosis
syndrome, multifocal choroiditis, angioid streaks, and
pathological myopia, PEDs are virtually never seen.
An explanation for the presence of large PEDs in pa-
tients with polypoidal CNV is not clearly understood; nor
is it clear why some patients with AMD have a very loose
RPE, putting them at risk for large detachments. In our
previous series, about one third of all patients with newly
diagnosed neovascularized AMD had a serous PED.
Other reports have implicated increasing lipid de-

Figure 5. A. Clinical photograph of a 71-year-old white man with a submacular hemorrhage. The macula of the fellow eye is normal. B. The early indocyanine
green (ICG) angiogram reveals multifocal areas of intense hyperfluorescence beneath the submacular hemorrhage. C. The late ICG angiogram shows a polypoidal
choroidal vascular abnormality that extends from the submacular hemorrhage temporally to the subfoveal region. The polypoidal lesions are beneath a slightly
larger pigment epithelial detachment. The nasal staining beneath the hemorrhage is due to active polypoidal neovascularization. The visual acuity is 20/100 OD.
D. The same patient 4 years after laser treatment of the active polypoidal choroidal neovascularization. There is an atrophic laser scar and a portion of the
polypoidal choroidal vascular membrane beneath the fovea. The visual acuity is 20/25 OD. E. The late-stage ICG angiogram taken at this time reveals persistent
staining of the subfoveal polypoidal choroidal vascular neovascularization beneath a flat macula.
posits in Bruch’s membrane as a causative factor for a PED in patients with soft drusen. Following an age-associated exponential curve, lipid theoretically reduces the hydraulic conductivity of the inner aspects of Bruch’s membrane. Pigment exudative detachments seem to occur at an earlier age in central serous chorioretinopathy and PCV. Accordingly, a PED is not likely to be exclusively the result of Bruch’s membrane impedance in these disorders. Choroidal hyperpermeability in central serous chorioretinopathy and leakage from large inner choroidal polypoidal lesions in PCV may explain the predilection for PED formation in these disorders that affect younger individuals.

Thus, based on the data in our study, PCV should be suspected in an elderly patient, male or female, with any of the following findings: (1) nonwhite patient, (2) peripapillary CNV, and (3) few or no drusen in the fellow eye of a unilateral case.

Why is it essential to recognize this PCV in elderly patients? To begin with, existing guidelines for laser photocoagulation treatment of CNV apply only to patients with classic CNV. Unfortunately, the vast majority of newly diagnosed patients have occult CNV. Patients with PCV seem to have completely different risk factors, clinical features, natural course, and visual outcomes than patients with AMD. Individuals with PCV are also likely to require a different therapeutic approach, whether one considers conventional laser photocoagulation or any of the other alternative therapies currently under investigation. Laser treatment of polypoidal CNV has been reported to be presumptive, empirical, and anecdotal, but rational. Photocoagulation of the leaking polypoidal lesions that present as focal, intense hyperfluorescence with late ICG staining has been associated with dramatic resolution of the associated serosanguineous complications and restoration of vision in an uncontrolled series of patients at our institution. The technique for this laser treatment, as previously reported, is similar to the method used for photocoagulation of a leaking retinal arteriolar macroaneurysm. Unlike classic CNV, where it is necessary to treat the entire neovascularized complex with an intense, confluent burn, only a mild thermal reaction to the leaking

Figure 6. A, Clinical photograph of a 67-year-old white woman with a submacular hemorrhage and a few areas of pigment epithelial atrophy and soft drusen formation. The visual acuity is 20/100 OS. B, The indocyanine green angiogram shows a focal area of intense hyperfluorescence or “hot spot” in the papillomacular bundle. C, Magnified view of the hot spot in the papillomacular bundle reveals small vascular projections in the inner plane of the choroid as well as anteriorly beneath the pigment epithelial detachment, terminating in aneurysmal or polypoidal lesions. D, Very late-stage angiogram shows that the hot spot in the papillomacular bundle is continuous with a collarette of polypoidal vascular lesions encircling the superior peripapillary region. E, Clinical photograph of the same patient 2½ years later following laser treatment to the hot spot but not the complete polypoidal choroidal vascular abnormality. There is an atrophic scar at the laser site and total resolution of the serosanguineous detachment. The visual acuity is 20/40 OS.
active polypoidal lesion is necessary to induce a fibrotic closure or infarction of the vascular abnormality and resolution of the associated exudative manifestations. Laser photocoagulation of active polypoidal lesions and thermal infarction of their corresponding feeding vessels without stimulation or fertilization of the rest of the vascular abnormality seems to be the mechanism responsible for effective therapy (Figure 5). Treatment of polypoidal CNV was the likely reason (at least in the illustrated cases) for successful ICG-guided laser treatment of “feeder vessels,” recently reported by Shiraga et al and Freund et al in a series of 37 Japanese patients. Such laser treatment is of particular interest when there is a large, subfoveal hemorrhage and an eccentric, leaky, active polypoidal lesion. The quick resolution of subfoveal blood and exudate in the central macula can reduce the neurotoxic effects of blood on the neurosensory retina, potentially avoid subfoveal tractional mechanical abnormalities, reestablish normal physiological RPE choroidal transport barriers and relationships, reduce retinal hypoxia and hypoglycemia, and possibly eliminate the likelihood of disciform or fibrovascular scarring, essentially preserving or restoring macular function.

It is also interesting that a retrospective review of 2 of our previously reported series on ICG-guided treatment revealed that several patients who had favorable results following photocoagulation therapy (Figure 6) actually had PCV lesions rather than occult CNV. At the time of those publications, we were simply not aware that polypoidal CNV could simulate neovascularized AMD in the central macula. We can speculate that the same relationship may exist for other uncontrolled series of ICG-guided laser treatment with similar results from other institutions.

While it seems as if polypoidal CNV can be effectively treated with ICG-guided laser to active polypoidal lesions, this approach cannot be recommended based on our present study. Like the potentially gratifying response to laser treatment of the aneurysmal lesions, the natural course of polypoidal CNV also seems to be favorable. We are aware of several patients who have had multiple polypoidal bleeds with spontaneous resolution of the associated detachments and preservation of good central vision, particularly when the bleeding was from the peripapillary area. Some patients even experience dramatic involution or even autoinfarction of the membrane (Figure 7). Accordingly, future studies are needed in the form of prospective randomized clinical trials to establish the precise natural course and the efficacy and safety of laser treatment of active polypoidal lesions in polypoidal CNV.

In the meantime, it is important for ophthalmologists to be aware that there are at least 3 forms of CNV that may be present, singularly or in combination, in elderly patients. First, new vessel formation in AMD may occur with active proliferation secondary to the growth of small capillaries from the choriocapillaris into Bruch’s membrane. When well-demarcated with fluorescein angiography, these vessels are classified as classic CNV; when ill-defined, as occult CNV. Now we must also consider polypoidal CNV as a third type of neovascularization in a measurable percentage (7.8% based on this study) of elderly patients of both sexes and all races. New study guidelines for the investigation of alternative approaches to treatment of neovascularized AMD should incorporate the clinical, prognostic, and therapeutic implications of all 3 forms of neovascularization as distinct entities and in combinations.

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Reprints: Lawrence A. Yannuzzi, MD, Vitreous-Retina-Macula Consultants of New York, 519 E 72nd St, Suite 203, New York, NY 10021.