Toward a Specific Classification of Polypoidal Choroidal Vasculopathy: Idiopathic Disease or Subtype of Age-Related Macular Degeneration

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Purpose. To suggest a clinical distinction between idiopathic polypoidal choroidal vasculopathy (PCV) and secondary polyps associated with neovascular age-related macular degeneration (NV-AMD).

Methods. The study was a retrospective case series of 52 eyes of 52 consecutive patients (31 females and 21 males) diagnosed with PCV. Initial diagnosis was based on scanning laser ophthalmoscope–indocyanine green angiography (SLO-ICGA) in association with fluorescein angiography (FA) and optical coherence tomography (OCT). All the data and images were analyzed in a masked fashion by four experienced examiners in two different sessions: the first, to classify patients into the two hypothesized groups (idiopathic polyps or NV-AMD–related polyps); the second, following a predetermined scheme, to describe objective features. The results obtained in each session underwent a cross multivariate analysis to identify statistically significant differences ($P \leq 0.05$) between the two groups.

Results. The two groups were clinically different on the basis of FA (leakage origin [$P = 0.001$] and presence of drusen [$P = 0.001$]), ICGA (evidence of choroidal neovascularization [CNV; $P = 0.001$] and/or branching vascular network [BVN; $P = 0.001$]), OCT imaging (type of pigmented epithelium detachment [$P = 0.001$], presence of BVN [$P = 0.001$], and subfoveal choroidal thickness [$P = 0.001$]). Further significant differences were observed according to the location of lesion (uni- or multifocal) ($P = 0.001$), type of CNV ($P = 0.001$), and best-corrected visual acuity ($P = 0.001$).

Conclusions. Our study demonstrated clinical and statistically significant differences between idiopathic PCV and NV-AMD–related polyps that could be considered as distinct entities. Although they share some similarities, mainly the sub-RPE location, the ability to identify a specific clinical pattern suggests a more specific therapeutic approach for these two entities.

Keywords: age-related macular degeneration (AMD), choroidal abnormal network, choroidal thickness, enhanced depth imaging (EDI), en face optical coherence tomography (OCT), polypoidal choroidal vasculopathy, choroidal abnormal network, type 1 choroidal neovascularization (CNV)

The diagnosis of polypoidal choroidal vasculopathy (PCV) is based on the indocyanine green angiography (ICGA) evidence of a polypoidal choroidal vascular lesion appearing during the midphase, usually associated with an abnormal branching vascular network (BVN), as described by the Japanese Study Group (2005).[1] This appearance is frequently correlated with elevated orange-red lesion(s) observed on fundus examination. Optical coherence tomography (OCT) is very helpful in the identification of these polyps, frequently multifocal and located not only at the macula but also around or at some distance from the optic disc.[2] The widely used spectral-domain OCT (SD-OCT) has a critical role in the detection of the associated serous or serosanguineous, variably sized detachment of the neurosensory retina and the retinal pigment epithelium (RPE). Also, enhanced depth imaging (EDI) SD-OCT demonstrates a frequent thickening of the underlying choroid in PCV.[3]

Polypoidal choroidal vasculopathy was first presented as a specific condition by Yannuzzi at the Macula Society Meeting in 1982 and the study was published in 1990.[4] The entity was initially called "idiopathic PCV" designating polypoidal, subretinal, vascular lesions associated with a serous and hemorrhagic pigmented epithelium detachment (PED). Kleiner et al.[5] subsequently described, at the Annual Meeting of the American Academy of Ophthalmology in 1984, an entity termed "posterior uveal bleeding syndrome." Also, Stern et al.[6] have described a group of middle-aged African American women with hemorrhagic detachments of the pigment epithelium and neurosensory retina.

The initial description of this entity insisted on its specificities, reporting it as a separate clinical entity, with a distinct abnormality of the choroidal vasculature, different from "wet" or neovascular AMD and other diseases associated with subretinal neovascularization. However, in the early nineties, some experts started reporting PCV with an "expanded spectrum."[2,7–10] This categorization of PCV either as a subtype of neovascular AMD (NV-AMD) or as a different disease entity highlights the controversy regarding the definition of the disease itself.

The purpose of this study was to address this controversy in order to assess the differences in epidemiology, clinical presentation, and imaging between these two separate entities that differentiate them from each other. A clinical distinction could be made between idiopathic PCV and polyps associated with NV-AMD. More importantly, considering these two as specific and individual entities may lead to significant consequences regarding the treatment and outcomes after treatment.

Materials and Methods

Subjects

In our retrospective case series, 52 eyes of 52 consecutive European (Caucasian) patients diagnosed with PCV in our center between September 30, 2013, and June 30, 2014, were enrolled in the study.

Study Design

Following a complete ophthalmic evaluation including ETDRS visual acuity testing, all eyes were imaged with macular SD-OCT (including B-scans, C-scans, and EDI patterns), autofluorescence, infrared and multicolor imaging, fluorescein angiography (FA), and ICGA.

Initial diagnosis of PCV was based on ICGA with scanning laser ophthalmoscope (SLO-ICGA, HRA-2; Heidelberg Engineering, Heidelberg, Germany), associated with typical clinical and fluorescein angiographic findings, and EDI SD-OCT (Spectralis HRA-OCT; Heidelberg Engineering), which allowed a possible clinical distinction between the two subtypes of polyps.

Two masked retinal specialists (FC, OS), experienced in the assessment and management of PCV, classified the whole sample into two main subgroups (patients with NV-AMD–related polyps and patients with idiopathic polyps) and then compared their results to analyze possible discrepancies.

This distinction into two groups was made by identifying at least 6 of 10 different criteria including age, rapidity of evolution, presence of drusen, presence of one or multiple hemorrhagic PEDs, FA leakage from abnormal vessels, presence of BVN on ICGA (BVN is generally distinguished from a choroidal neovascularization [CNV] because it is perfused simultaneously with the choroid on ICGA and it presents no leakage on FA), suggestive changes in the OCT (bubble sign, double-layer sign, subfoveal choroidal thickness), macular or extramacular location, and uni- or multifocal lesion.

In a second session, all the data and the images of all the study patients (in a random order) were re-evaluated by a second set of experienced examiners (ML, FB), masked to the results of the previous classification, following a predetermined scheme based on demography and imaging (FA, ICGA, and OCT).

Each case of polypoidopathy was thoroughly described by considering several parameters: demography; location (macular/peripapillary); FA: leakage (polyps, BVN, CNV), drusen, lipids, or hemorrhages; ICGA: CNV network and its diameter (μm), BVN and its diameter (μm), polyp number, location and relationship to CNV/BVN; OCT: ellipsoid zone integrity, central macular thickness (CMT; μm), hyperreflective dots (HRDs), cystoid spaces, subretinal fluid (SRF), intraretinal dense areas, PED (type and height, μm), polyps' visibility, BVN, and subfoveal choroidal thickness (CT).

At the end of this second session, the data obtained were associated, case by case, with the results of the first session. This cross-comparison and consequential multivariate analysis were developed by one of the coauthors (AD), an expert in statistics. The aim was to identify features, with an intergroup statistically significant difference, that could promote the distinction between the two hypothesized polypoidopathies: idiopathic polyps (with or without evidence of BVN) as opposed to polyps associated with CNV type 1 (or 2). In both sessions, in cases of possible interexaminer discrepancies, one of the coauthors (GC), extensively experienced in the diagnosis and treatment of PCV, was consulted to help take the final decision.

This study was conducted according to the tenets of the Declaration of Helsinki. The study protocol was approved by the Institutional Ethics Committee and all subjects gave fully informed consent.

Statistical Analysis

The measured visual acuity was converted to the logarithm of the minimum angle of resolution (logMAR) for statistical analyses. For data analysis, a spreadsheet on Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) and SPSS for Windows software (version 17.0; SPSS, Inc., Chicago, IL, USA) were used. The Mann-Whitney U test was used for continuous variables. The χ^2 and Fisher's exact tests were used for categorical variables. A statistical significance level of 0.05 was required.

Results

We enrolled 52 patients, of whom 34 (65.4%) were categorized as having idiopathic polyps and 17 (32.7%) as having NV-AMD polyps after the first analytical session. One patient (1.9%) was excluded from this categorization because of a clear association between the polyps and a diffuse retinal epitheliopathy (Table 1).

In the second imaging analysis session, performed by different examiners, the data and images of each subject were classified by following a predetermined scheme. Demography is reported in Table 2. Imaging and additional data (FA, ICGA, OCT) are reported in Tables 3 through 6. All the data that showed a statistically significant difference between the two study groups are reported in the following paragraphs; all the others are summarized in Tables 2 through 6.

Fluorescein Angiography

Leakage only from the polyps was present in 37/51 (72.5%) patients, from both polyps and CNV in 12/51 (23.5%) patients, and only from the CNV in 2/51 (4%) patients. In the idiopathic group, all the patients (100%) had leakage only from the polyps, while in the NV-AMD group, 12/17 (70.6%) patients had leakage from both the polyps and CNV, 3/17 (17.6%) only from the polyps, and 2/17 (11.8%) only from the CNV ($P = 0.001$; Figs. 1, 2).

Drusen were present in all (100%) patients in the NV-AMD group, while they were present in only 5/34 (14.7%) patients in the idiopathic group ($P = 0.001$).

Indocyanine Green Angiography

A CNV network was identified on ICGA in 17/51 (33.3%) patients, while it was not detectable in 34/51 (66.7%) patients. A CNV network was identified in all (100%) NV-AMD patients,

Table 1. Frequency (Percentage) of Patients With Idiopathic Polyps and NV-AMD–Related Polyps

Etiology	Frequency	Percentage	Valid Percentage	Cumulative Percentage
Idiopathic polyps	34	65.4	65.4	65.4
NV-AMD polyps	17	32.7	32.7	98.1
Other	1	1.9	1.9	100

Table 2. Multivariate Analysis of Demographic Data

	Etiology			
	Idiopathic Polyps, n (%)	NV-AMD Polyps, n (%)	Total, n (%)	*P* Value
Age, mean ± SD, y	73.8 ± 9	76 ± 8.5	74.3 ± 8.8	0.424
Sex				
Male	15 (44.1)	5 (29.4)	20 (39.2)	0.311
Female	19 (55.9)	12 (79.6)	31 (60.8)	

while no one in the idiopathic group showed a CNV network ($P = 0.001$). The mean CNV network diameter in NV-AMD patients was 3292.1 ± 1541.9 μm. The presence of BVN was observed in 31/51 (60.8%) patients. There were no cases of BVN in any of the NV-AMD groups, while BVN was observed in 31/34 (91.2%) patients in the idiopathic group ($P = 0.001$). The mean BVN diameter in the idiopathic group was 1647.5 ± 913.3 μm (Figs. 1, 2).

Optical Coherence Tomography

Pigmented epithelium detachment was detectable in all 51 (100%) patients, either serous in 35/51 (68.6%) patients, hemorrhagic in 6/51 (11.8%), or fibrovascular in 10/51 (19.6%) patients. In the NV-AMD group, PED was serous in 7/17 (41.2%) patients, hemorrhagic in 1/17 (5.9%), and fibrovascular in 9/17 (52.9%). In the idiopathic group, PED was serous in 28/34 (82.4%) patients, hemorrhagic in 5/34 (14.7%), and fibrovascular in 1/34 (2.9%) ($P = 0.001$; Table 5). The mean PED height was 241.4 ± 179.3 μm. In the NV-AMD group, mean PED height was 265.0 ± 126.6 μm, while it was 232.3 ± 203.3 μm in the idiopathic group ($P = 0.097$).

Branching vascular network was detected in 28/51 (54.9%) patients. Branching vascular network was not observed in any NV-AMD patient. In the idiopathic group, BVN was present in 28/34 (82.4%) patients ($P = 0.001$).

Mean subfoveal CT was 246.6 ± 101.1 μm. In the NV-AMD group, mean subfoveal CT was 176.6 ± 62.6 μm, while it was 278.3 ± 99.9 μm in the idiopathic group ($P = 0.001$; Figs. 1, 2).

Additional Data

In the entire group of study patients, a type I CNV was identified in17/51 (33.3%) patients. All the NV-AMD patients had a type I CNV, while no one in the idiopathic group had any evidence of CNV ($P = 0.001$). The pathologic condition was unifocal in 42/51 (82.4%) patients and multifocal in 9/51 (17.6%). All the NV-AMD patients had unifocal involvement, while 25/34 (73.5%) idiopathic patients had unifocal involvement and 9/34 (26.5%) had a multifocal one ($P = 0.021$). Finally, the mean best-corrected visual acuity (BCVA) in logMAR for the whole sample was 0.48 ± 0.33 (range, 0.10–1.51). It was 0.58 ± 0.29 in the NV-AMD group compared with 0.43 ± 0.35 in the idiopathic group ($P = 0.036$).

Discussion

Since the first description of PCV in 1982 by Yannuzzi et al.,[4] more than 3 decades have passed and PCV is now a well-recognized disease with a specific pattern. Numerous studies based on imaging, histopathology, and genetics are gradually revealing its pathogenesis, although a recent controversy remains to be solved: is the PCV a variant of type 1 NV-AMD or a specific idiopathic entity? In favor of the hypothesis of a variant of type I NV-AMD, it has been suggested that BVN is a neovascularization and that this neovascularization is located between the Bruch's membrane and the RPE layer, similar to the location of CNV type I in AMD.[2,9,10] On the contrary, although there is emerging evidence of common molecular genetic determinants involving complement pathway and common environmental risk factors, there are several significant differences between PCV and NV-AMD in epidemiology, clinical and angiographic features, and histopathology as well as in the response to anti-VEGF therapy.[11,12]

Table 3. Multivariate Analysis of FA Data

	Etiology			
	Idiopathic Polyps, n (%)	NV-AMD Polyps, n (%)	Total, n (%)	*P* Value
Leakage				
Polyps	34 (100)	3 (17.6)	37 (72.5)	0.001*
CNV	0 (–)	2 (11.8)	2 (3.9)	
Mixed	0 (–)	12 (70.6)	12 (23.5)	
Drusen				
Absent	29 (85.3)	0 (–)	29 (56.9)	0.001*
Present	5 (14.7)	17 (100)	22 (43.1)	
Lipids				
Absent	27 (79.4)	14 (82.4)	41 (80.4)	0.99
Present	7 (20.6)	3 (17.6)	10 (19.6)	
Hemorrhages				
Absent	25 (73.5)	15 (88.2)	40 (78.4)	0.297
Present	9 (26.5)	2 (11.8)	11 (21.6)	

* Statistically significant *P* values.

Table 4. Multivariate Analysis of ICGA Data

	Etiology			
	Idiopathic Polyps, n (%)	**NV-AMD Polyps, n (%)**	**Total, n (%)**	***P* Value**
CNV evidence				
Absent	34 (100)	0 (–)	34 (66.7)	0.001*
Present	0 (–)	17 (100)	17 (33.3)	
Mean CNV network diameter, μm	–	3292.1 ± 1541.9	–	–
BVN evidence				
Absent	3 (8.8)	17 (100)	20 (39.2)	0.001*
Present	31 (91.2)	0 (–)	31 (60.8)	
Mean BVN diameter, μm	1647.5 ± 913.3	–	–	–
Polyp No.				
1	9 (26.5)	4 (23.5)	13 (25.5)	0.808
≥2 to ≤5	20 (58.8)	12 (70.6)	32 (62.7)	
>5	5 (14.7)	1 (5.9)	6 (11.8)	
Polyp location				
Macular (M)	20 (58.8)	16 (94.1)	36 (70.6)	NS
Extramacular (E)	2 (5.9)	0 (–)	2 (3.9)	
Peripapillary (P)	3 (8.8)	0 (–)	3 (5.9)	
M + E	3 (8.8)	0 (–)	3 (5.9)	
M + P	4 (11.8)	1 (5.9)	5 (9.8)	
E + P	1 (2.9)	0 (–)	1 (2)	
M + E + P	1 (2.9)	0 (–)	1 (2)	
Polyps/BVN-CNV				
Absent	3 (8.8)	0 (–)	3 (5.9)	0.179
Inside	27 (79.4)	17 (100)	44 (86.3)	
Outside	4 (11.8)	0 (–)	4 (7.8)	

NS, not significant.
* Statistically significant *P* values.

In our study, we collected and analyzed in detail all the data that could specifically define the disease and evaluated the possibilities to assess the differences in epidemiology, clinical presentation, and imaging. Moreover, we evaluated the statistically significant distinction between idiopathic PCV and polyps related to NV-AMD.

After a careful analysis focused on the demographic, clinical, and imaging data, we identified 34 patients with idiopathic polyps, 17 with NV-AMD–related polyps, and we excluded from our study analysis a single patient who had a clear association with concomitant retinal diffuse epitheliopathy.

The prevalence of PCV in white (Caucasian) patients has been reported to be between 4% and 9.8% in published literature, while it seems to be substantially higher in Asian patients.[10,13–17] Some studies have reported that 54.7% of patients have polyps in the course of NV-AMD in Japan and that these data could be an underestimate because they do not include a significant number of asymptomatic subjects with polyps in a quiescent or regressed stage.[2,18] Considering this, and in order to avoid potential bias due to the variable incidence of PCV in different races, only European Caucasian patients were enrolled in the present study.

The age at diagnosis can range from the twenties to the eighties, but PCV is most commonly diagnosed between the ages of 60 and 70 years (generally earlier than typical NV-AMD).[2] Most European patients with PCV are female (75%), while the opposite is true for Asians (71% male).[2] Recently, the female prevalence (65.6%) in PCV has been emphasized as well as the fact that patients with a diagnosis of PCV are 10 years younger than those with CNV type I.[19]

In our study sample of 51 patients, we analyzed data related to age, sex, and ethnic differences in the two groups (idiopathic versus NV-AMD related) and found no statistically significant differences.

In 92% of the Asian patients, PCV occurs in the central macular area, whereas there is an equal distribution of macular and peripapillary location in Europeans.[2] Our study showed, as expected, unifocal involvement of the macular area in all patients in the NV-AMD group, while 26.5% of the patients with idiopathic polyps had a multifocal distribution. All these data seem to suggest an important genetic substrate between different races, but it should be considered that quiescent, small, or asymptomatic lesions could be misdiagnosed especially if they are without macular involvement.

Many authors have suggested that FA is not as useful in imaging PCV as it is in other forms of neovascularization.[2] However, only FA can indicate the presence or absence of leakage, either from the actual CNV or from the BVN.[20] Regarding leakage, we found a statistically significant difference between the two groups: all our patients identified as idiopathic showed leakage only from the polyps with no evidence of leakage from the BVN or any other structures. On the contrary, many NV-AMD patients showed leakage from the CNV alone or in association with leaking polyps (82.4%, $P = 0.001$).

The presence of significant drusen is reported in the literature as varying between 16.7% and 24% in patients affected by PCV in, at least, one eye.[2,18] In our study, drusen was present in the whole NV-AMD group (100%), but in only 14.7% of the idiopathic group ($P = 0.001$).

In a study involving 65 eyes of 44 patients, ICGA reveals the presence of BVN in 68.7% of the cases using a confocal-SLO

Table 5. Multivariate Analysis of OCT Data

	Etiology			
	Idiopathic Polyps, n (%)	**NV-AMD Polyps, n (%)**	**Total, n (%)**	***P* Value**
Ellipsoid integrity				
Absent	32 (94.1)	17 (100)	49 (96.1)	0.547
Present	2 (5.9)	0 (–)	2 (3.9)	
HRDs				
Absent	0 (–)	0 (–)	0 (–)	0.122
Retinal	20 (58.8)	14 (82.4)	34 (66.7)	
Choroidal	0 (–)	0 (–)	0 (–)	
Retinal + choroidal	14 (41.2)	3 (17.6)	17 (33.3)	
Cystoid spaces				
Absent	24 (70.6)	10 (58.8)	34 (66.7)	0.401
Present	10 (29.4)	7 (41.2)	17 (33.3)	
SRF				
Absent	8 (23.5)	4 (23.5)	12 (23.5)	0.99
Present	26 (76.5)	13 (76.5)	39 (76.5)	
IRDAs				
Absent	15 (44.1)	6 (35.3)	21 (41.2)	0.763
Present	19 (55.9)	11 (64.7)	30 (58.8)	
PED type				
Absent	0 (–)	0 (–)	0 (–)	0.001*
Serous	28 (82.4)	7 (41.2)	35 (68.6)	
Hemorrhagic	5 (14.7)	1 (5.9)	6 (11.8)	
Fibrovascular	1 (2.9)	9 (52.9)	10 (19.6)	
Mean PED height, μm	232.3 ± 203.3	265 ± 126.6	241.4 ± 179.3	0.097
Polyps evidence				
Absent	0 (–)	0 (–)	0 (–)	NS
Present	34 (100)	17 (100)	51 (100)	
BVN evidence				
Absent	6 (17.6)	17 (100)	23 (45.1)	0.001*
Present	28 (82.4)	0 (–)	28 (54.9)	
CMT, μm	348.6 ± 112.7	336.4 ± 115.1	342.8 ± 112.1	0.682
Macular involvement CMT, μm	365.7 ± 108.2	336.4 ± 115.1	353 ± 110.2	0.352
CT, μm	278.3 ± 99.9	176.6 ± 62.6	246.6 ± 101.1	0.001*

* Statistically significant *P* values.

Table 6. Multivariate Analysis of Additional Data

	Etiology			
	Idiopathic Polyps, n (%)	**NV-AMD Polyps, n (%)**	**Total, n (%)**	***P* Value**
CNV type				
Absent	34 (100)	0 (–)	34 (66.7)	0.001*
Type I	0 (–)	17 (100)	17 (33.3)	
Type II	0 (–)	0 (–)	0 (–)	
Type III	0 (–)	0 (–)	0 (–)	
Pattern				
Typical	29 (85.3)	15 (88.2)	44 (86.3)	0.99
Atypical	5 (14.7)	2 (11.8)	7 (13.7)	
Foci No.				
Unifocal	25 (73.5)	17 (100)	42 (82.4)	0.021*
Multifocal	9 (26.5)	0 (–)	9 (17.6)	
BCVA, logMAR	0.43 ± 0.35	0.58 ± 0.29	0.48 ± 0.33	0.036*

* Statistically significant *P* values.

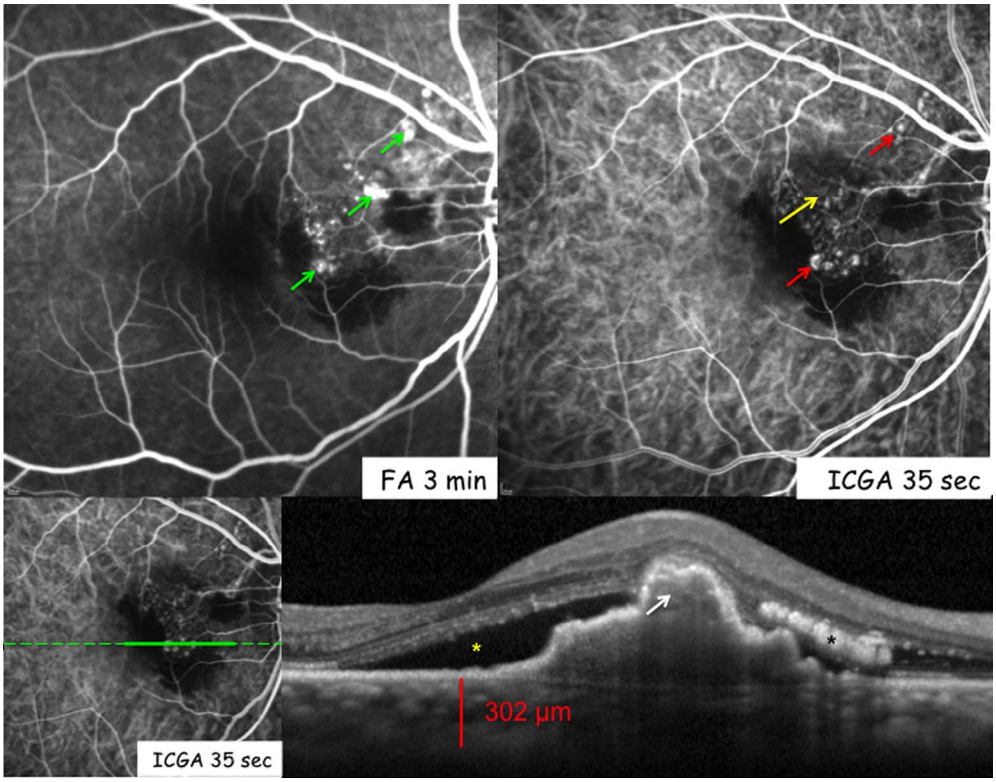

Figure 1. Angiographic and tomographic features in a case of idiopathic polyps. Fundus FA (*top left*) and ICGA (*top right*). The FA (*top left*) shows a PED associated with an area of masked fluorescence and multiple hyperfluorescent spots (*green arrows*). In the early venous phase, ICGA (*top right*) reveals multifocal hyperfluorescent spots (*red arrows*) corresponding to active polyps at the border of an extensive BVN (*yellow arrow*). In the *bottom left image* (early venous phase ICGA, 35 seconds), the correlation is shown between the polypoidal lesions and their location on ICGA. On the *bottom right*, SD-OCT shows a peaked PED arising in the perifoveal area and the typical "bubble sign" (*white arrow*), probably representing the polyp lumen, attached to the posterior surface of the PED. Intraretinal hyperreflective large confluent dots (*black star*) are probably related to hard exudates. A hyporeflective area suggests subretinal fluid accumulation (*yellow star*). Choroidal subfoveal thickness (302 µm) is highlighted (in *red*).

(cSLO) system and in 60.4% using a fundus camera.[21] In our study, early ICGA phases revealed the presence of BVN in 31/51 (60.8%) patients: None of the 17 NV-AMD patients had evidence of BVN, while in the idiopathic group 31 of 34 patients had BVN (91.2%, $P = 0.001$). This observation is in accordance with a previous publication[22] from 2005, which suggests that PCV is mainly associated with inner choroidal vascular abnormalities that show focal dilation, constriction, and tortuosity of vessels comprising branching three-dimensional networks, rather than the pattern of neovascular tissue (CNV). In our study, we found a clear ICGA type I CNV network in 17 cases (33.3%); all the type I CNV cases identified were in the NV-AMD group with none in the idiopathic group ($P = 0.001$).

Optical coherence tomography is critical in the diagnosis of PCV. A recently published study[19] has shown that specificity for the detection of PCV using SD-OCT was 92.9%, with sensitivity of 94.6% and positive and negative predictive values of 97.2% and 86.7%, respectively. Four tomographic diagnostic criteria have been considered to make a definite diagnosis of PCV: a sharp PED peak, a PED notch, a visible hyporeflective lumen within hyperreflective lesions adherent to the outer surface of the RPE, and multiple PEDs.[2,3,23] The presence of BVN, using a time-domain OCT, has been reported in 59% of the cases.[24] Other authors have shown that vascular abnormalities of PCV (polypoidal lesion and BVN) are visualized on SD-OCT images in 95% of the cases, as areas of moderate reflectivity between the clearly delineated abnormal section of RPE and Bruch's membrane (double-layer sign).[23] According to previously described OCT criteria,[24] we identified the presence of BVN in 54.9% of the whole sample. Considering the idiopathic group, BVN was evident in 82.4% of the cases, while there was no BVN in any of the NV-AMD–related cases. Our results are consistent with previous publications highlighting the capability of SD-OCT to detect the presence of BVN and help to differentiate it, while associated with polypoidal lesions, from a type I CNV.[23]

Some authors have addressed the presence and features of PED in PCV.[2,12] In a study on 93 eyes, PED is observed in 51 cases (55%) of which 5 are hemorrhagic (9.8%) and 46 (90.2%) serous.[25] In our study, a variable height PED was present in all 51 patients, probably owing to the active stage of the lesion in which they were evaluated. Also, we observed a statistically significant difference in the various subtypes of PED: There was an evident prevalence of serous (or serohemorrhagic) PED in the idiopathic group, while more than half of the NV-AMD–related polyps showed a fibrovascular one (Table 5).

From published literature,[26] we identified subfoveal CT as an important and objective parameter to validate our thesis. We, therefore, calculated the mean subfoveal CT: this was 278.3 ± 99.9 µm in the idiopathic group, more than 100 µm thicker than in the NV-AMD group (176.6 ± 62.6 µm) ($P = 0.001$). These results are consistent with those reported by Kawamura et al.[26] Their classification of PCV type 1 (CNV) and PCV type 2 (choroidal vasculature abnormalities) is also based on the observation of a significant difference in choroidal thickness between the two entities (199 ± 65 and 288 ± 98 µm, for types I and II, respectively).

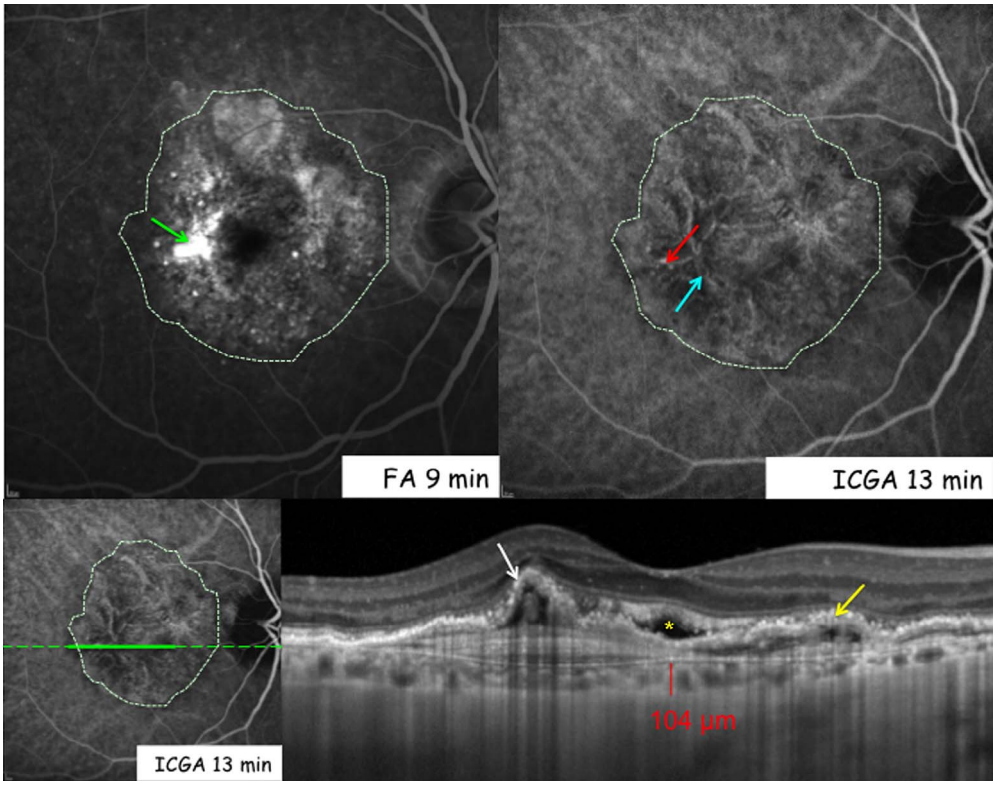

Figure 2. Angiographic and tomographic features in a case of NV-AMD–related polyps. The FA (*top left*) shows a wide macular lesion (*dashed light-green line*) including a focal leaking area (*green arrow*). In the intermediate phase, ICGA (*top right*) reveals several hyperfluorescent spots (*red arrow*), probably corresponding to the active polyp site, with many remnant vessels (*cyan arrow*) of an extensive CNV (type I, *dashed light-green line*). On the *bottom left*, ICGA (13 minutes) shows occult subepithelial new vessels converted into a well-defined network. On the *bottom right*, SD-OCT shows a narrow peaked PED, probably corresponding to the polypoidal lesion (*white arrow*) arising from an extensive fibrovascular PED (*yellow arrow*). Subretinal hyporeflective spaces (*yellow star*) suggest fluid accumulation. Choroidal subfoveal thickness of only 104 µm is highlighted (in *red*).

Spaide,[27] using EDI OCT, has found decreased choroidal thickness, pigmentary changes, and a paucity of visible choroidal vessels in elderly patients; these changes have been called "age-related choroidal atrophy." Another recent study[28] has highlighted the differences in subfoveal choroidal thickness between adult-onset foveomacular vitelliform dystrophy (AOFVD) and AMD: the significant difference in thickness (325.66 ± 85.98 µm in AOFVD versus 158.55 ± 57.87 µm in NV-AMD) suggests a probable different pathogenic mechanism between the two clinical entities. Choroidal thickening in eyes with PCV and thinning in eyes with exudative AMD have been found with SD-OCT.[3] Also, the choroid in the asymptomatic fellow eye of a PCV patient is markedly thickened, even if angiographically active lesions suggestive of PCV are not detected. Considering these observations, the authors hypothesize the possibility of different pathogenic mechanisms affecting PCV and exudative AMD and indirectly support the hypothesis that PCV may not be a subtype of AMD.

The presence of unexpected good visual acuity (BCVA) in patients affected by PCV has already been highlighted.[2] This disparity between the severity of the serosanguineous detachments and good vision was explained by the observed minimal intraretinal changes. We found a statistically significant difference in visual acuity between our two study groups, with 0.43 logMAR in the idiopathic group versus 0.58 logMAR in the NV-AMD group. We believe that this difference is due to the lower frequency of central foveal involvement, a major cause of visual impairment, in the idiopathic group.

Histopathologic examination of polypoidal lesions—although it is difficult to obtain human specimens—could help elucidate the pathogenesis of these lesions.

In a recent publication examining the histopathology of five PCV specimens from five eyes, focal hyalinization of choroidal vessels is reported along with extensive replacement of the smooth muscle component by amorphous pseudocollagenous tissue. This suggests arteriosclerotic changes not only in the choroid, but also in other parts of the body.[29] Moreover, the vascular endothelial cells in the PCV specimens are negative for VEGF.[29] These observations are consistent with a study of aqueous levels of VEGF in eyes with PCV; these levels are significantly lower than in eyes with exudative AMD.[30]

Genetic factors play an important role in the pathogenesis of AMD. As AMD and PCV share similarities, the genes involved in AMD have been investigated in PCV to see if these genes could play a role in PCV and also if the differences between the two could help classify PCV as a subtype of AMD or as a distinct disease. Several genes associated with AMD have been analyzed in PCV, showing significant associations such as rs10490924 of *ARMS2*, Y402H of *CFH*, *CFB-C2*, and *C3* genes.[2,31,32] Considering *CFH*, other polymorphisms have also been investigated such as rs800292 (I62V), rs3753394, rs1329428, and rs1410996, showing association with PCV.[31,32] The single nucleotide polymorphism (SNP) rs10490924 of *ARMS2* is the most investigated SNP in PCV with an overall allelic odds ratio (OR) of 2.27.[31] Among the different genes reporting genetic associations with PCV, rs10490924 of *ARMS2* is the only polymorphism with significant differences between AMD and PCV.[33] Tanaka et

al.[32] have shown that the rs10490924 variant is associated with polypoidal CNV but not with typical PCV. Another study[34] reports that the pooled risk allele frequency is estimated as significantly higher in NV-AMD (64.7%) than PCV (55.6%). A meta-analysis has estimated the attributable risks for the variant allele as 43.9% and 29.7% for NV-AMD and PCV, respectively.[34]

Further, genotype–phenotype correlations have been analyzed in PCV. The rs10490924 of *ARMS2* is associated with the risk of vitreous hemorrhage,[35,36] but the association with sex, age of onset, bilateral involvement, and BCVA is more controversial.[31]

However, owing to the difference in the rs10490924 *ARMS2* gene allele frequency and the odds ratio between PCV and AMD, it appears that PCV could be a specific entity. Genetic results to date do not provide a definite answer to the controversy whether PCV is a subtype of AMD or a specific entity[37]; it just shows that AMD and PCV share only partially similar molecular mechanisms. Therefore, additional genetic and environmental factors might be implicated in the pathophysiology of PCV.

We are aware of the limits of this study, such as the limited number of patients, the retrospective approach, and the lack of association of our clinical findings with histologic or genetic evidence. Nevertheless, there were several statistically significant differences between the two initially hypothesized entities (NV-AMD with polyps and idiopathic polyps) when analyzing the clinical and imaging data, many of which are considered as main diagnostic criteria for PCV.

We believe that this distinction could provide useful guidelines for treatment. In the case of idiopathic polyps, the gold standard could be the use of PDT (full or half fluence)[12,38,39] precisely targeted at the polyps, in both the macular and, if required, extramacular areas. Anti-VEGF injections can be additionally used to rapidly improve BCVA by reducing the accumulated fluid. On the other hand, for the NV-AMD polyps, the treatment could consist of repeated anti-VEGF injections with the eventual use of limited PDT to target the polyps in order to reduce hemorrhagic risk. Therefore, considering this potential difference in therapeutic approach, one could regard idiopathic polyps as a specific condition rather than a variant of type I CNV, and only one member in the large family of hemorrhagic maculopathies.

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