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POLYPOIDAL CHOROIDAL NEOVASCULARIZATION VERSUS TYPE 1 CHOROIDAL NEOVASCULARIZATION IN AGE-RELATED MACULAR DEGENERATION

A Fractal Analysis Study

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Purpose: To compare quantitative optical coherence tomography angiography parameters between polypoidal choroidal neovascularizations (PCNVs) and Type 1 choroidal neovascularizations (CNVs) in patients with age-related macular degeneration.

Methods: PCNV and Type 1 CNV lesions were retrospectively recruited in a cohort of patients with age-related macular degeneration. All the patients underwent a comprehensive ophthalmic evaluation, including best-corrected visual acuity, fluorescein and indocyanine green angiography, structural optical coherence tomography (OCT), and optical coherence tomography angiography.Vascular perfusion density, fractal dimension, and lacunarity were computed by means of fractal analysis of neovascular en face optical coherence tomography angiography slabs.

Results: Sixty-eight eyes were included in the analysis. Of them, 35 of 68 eyes (51.5%) had PCNV and 33 of 68 (48.5%) had Type 1 CNV. Patients with PCNV were significantly younger ($P = 0.0003$) and had a higher best-corrected visual acuity ($P < 0.0001$). The mean vascular perfusion density was 0.83 ± 0.11% in PCNVs and 0.46 ± 0.10% in Type 1 CNVs ($P < 0.0001$). The mean fractal dimension was 1.44 ± 0.1 in PCNVs and 1.45 ± 0.09 in Type 1 CNVs ($P = 0.86$) while the mean lacunarity was 2.46 ± 1.03 in PCNVs and 1.86 ± 0.52 in Type 1 CNVs ($P = 0.006$).

Conclusion: PCNVs resulted to be more heterogeneous and characterized by higher vascular perfusion density and lacunarity values than Type 1 CNVs. These interesting findings seem to support the idea that PCNVs and Type 1 CNVs are two separate clinical entities. However, future studies based on optical coherence tomography angiography fractal analysis, but also involving other relevant parameters such as demographics, presentation, morphology on multimodal imaging, and response to treatment, are necessary before drawing any definitive conclusions on whether PCNV is a specific clinical entity or a neovascular age-related macular degeneration variant.

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Age-related macular degeneration (AMD) is considered the leading cause of central vision impairment in the elderly population, living in the Western world. One form of the late AMD is the neovascular AMD (nAMD), characterized by the occurrence of abnormal neovascular lesions causing exudative retinal changes, responsible for acute vision loss in approximately 90% of the AMD cases.[1]

Originally, such neovascular lesions were distinguished into two different forms, named Type 1 choroidal neovascularization (CNV) and Type 2 CNV, by Gass et al.[2] In 1982, Yannuzzi et al, first, provided the description of "polypoidal choroidal vasculopathy" (PCV) that was considered as a separate clinical entity, different from nAMD and other macular diseases that could be complicated by the development of subretinal

neovascularization. PCV is characterized by aneurysmal dilations (polyps) arising at the edges of the choroidal branching vascular network.[3] Newly, PCVs have been distinguished into two different types: Type 1 PCV, also called "polypoidal choroidal neovascularization" (PCNV), with a subretinal pigment epithelium (RPE) location and Type 2 PCV, also named "typical PCV," presenting a deeper localization, at the level of the choroidal layers.[4]

In the early nineties, some authors described PCNV as an expanded spectrum of nAMD, and in the latest classification by Spaide et al,[5] it was included in the Type 1 CNV group.

Although PCNV and Type 1 CNV seem to be characterized by the same risk factors and molecular genetic variants, they are different regarding the epidemiology, natural evolution, prognosis, and traditional multimodal imaging.[6]

Recently, optical coherence tomography angiography (OCTA), a noninvasive technique generating dye-free angiographic images with high resolution in some seconds, has turned out to be a useful tool in the identification of both PCNV and Type 1 CNV.[7–9] Qualitative OCTA features may be helpful to distinguish different types of neovascular lesions only when they are used in combination with other retinal imaging biomarkers.[10] To this regard, fractal analysis of OCTA images enables to generate quantitative biomarkers which can be used to objectively distinguish neovascular lesions showing different prognosis and long-term evolution.[11]

As far as we know, there are no previously published reports where fractal OCTA parameters from PCNVs and Type 1 CNVs have been compared to establish whether PCNV is a variant of nAMD. Therefore, the purpose of the current investigation was to assess the application of fractal analysis to both PCNV and Type 1 CNV to find an answer to the following question: Is PCNV a specific clinical entity or a nAMD variant?

Methods

This was a retrospective, observational study on active PCNV and Type 1 CNV cases seen at the Odeon Ophthalmology Center, Paris, France, and the Ophthalmology Unit, University of Sassari, Sassari, Italy, between February 2019 and December 2020.

The study was performed in compliance with the tenets of the Declaration of Helsinki for research involving human subjects, and all enrolled patients gave their written informed consent to participate.

PCNV and Type 1 CNV diagnosis was based on clinical and multimodal imaging features, including ophthalmoscopic examination, fluorescein angiography, indocyanine green angiography (ICGA; Heidelberg Engineering, Germany), and spectral domain OCT (SD-OCT; Heidelberg Engineering, Germany).[12–16]

The diagnostic criteria for Type 1 CNV were pigment epithelium detachment associated, or not, with subretinal detachment on SD-OCT, hyperfluorescent pin-points on late fluorescein angiography frames, visualization of neovascular lesions on intermediate ICGA frames, and late hypercyanescent plaque on ICGA.[13,15] Conversely, the diagnosis of the PCNV was performed when a typical branching vascular network and characteristic aneurysmal dilatations (polyps) were detected on ICGA.[3,12,14,16]

Patients with preexisting ophthalmological disorders, including uveitis, high myopia (refraction ≥ 6 diopters), a history of ocular trauma, and any other condition potentially confounding retinal image interpretation, were excluded.

All eligible patients underwent a complete ophthalmological evaluation that included best-corrected visual acuity (BCVA) measurement with Early Treatment Diabetic Retinopathy Study charts, multimodal imaging evaluation (fluorescein angiography, ICGA, and SD-OCT), and OCTA assessment with the swept source OCTA Triton (Topcon, Tokyo, Japan), AngioVue XRTVue Avanti (Optovue; Fremont, CA), or SPECTRALIS OCTA (SPECTRALIS; Heidelberg Engineering). The angiocube was centered on the PCNV or Type 1 CNV, and their features were analyzed and compared with ICGA.

Eyes with poor quality images on OCTA (signal strength index <60) secondary to eye movements, media opacities, and inadequate pupillary dilation were not considered for further analysis.

The signal-to-noise ratio was immediately improved by using the algorithm embedded in the OCTA

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devices, a postprocessing software that allows improvement of the image quality by removing artifacts potentially confounding image interpretation. Moreover, manual adjustment of the automatic segmentation was performed by two expert retina specialists (D.C. and A.P.) to correctly visualize the capillary plexus, outer retinal layers, and choriocapillaris and recognize precisely the neovascular plane. Specifically, manual adjustment of the thickness between two segmentations is of critical importance to improve the visualization of the neovascular lesion on the simultaneous en face angiogram. Slabs immediately below RPE detachment were excluded to limit projection artifacts.

Appearance and location of all PCNVs and Type 1 CNVs were then analyzed by two masked retina specialists (F.C. and R.S.) and compared with ICGA.

The en face outer retina OCTA slabs of PCNVs and Type 1 CNVs were exported into a previously validated custom graphical user interface, created by means of MATLAB (v.r2018a) coding language. Then, fractal analysis was performed to estimate quantitative parameters such as vascular perfusion density (VPD), fractal dimension (FD), and lacunarity (LAC).

The Otsu method[17] was used to binarize the OCTA images, whereas the speckle noise was removed by means of the application of a median filter of radius two pixels.[11,14,18] Moreover, isolated pixels, and groups of less than 10 connected pixels, were filtered and not considered for further analysis, thus limiting the potential bias because of projections artifacts. Then, the highest density zone was detected, and the density map was calculated. A graphical interface was used for the analysis of OCTA slabs to calculate quantitative parameters, including VPD, FD, and LAC.

VPD was defined as the ratio between the area of the perfused vasculature and the total image area, computed in a region of measurement, on the OCTA slab previously binarized.[11]

The box-counting method at multiple origins was applied to the binary skeleton image to calculate the vascular network FD and LAC, which are, respectively, global indices of morphological complexity and structural nonuniformity. In particular, the binary skeleton image was divided into square boxes of equal size, and the number of boxes containing a vessels segment was computed. Then, according to vessel distribution, the FD value ranged from 0 to 2. Lesions with higher pattern complexity are characterized by higher FD values.

Mathematical formulae were used to assess the pixel distribution in binary skeleton images and evaluate the nonuniformity of the lesions. Lesions with great heterogeneity show higher LAC values, whereas those with a homogenous vascular structure have lower LAC.[11]

Descriptive data are presented as numbers and % for categorical variables and means ± SD for quantitative parameters.

The analyzed data were presented as normal distribution (Shapiro–Wilk test); hence, the Student *t* test for continuous variables was used. *P* values <0.05 were considered to be statistically significant. Statistical analysis was performed using the Statistical Package for Social Sciences version 20.0 for Mac (IBM, Chicago, IL).

Results

Sixty-eight eyes of 68 patients with nAMD (44 men and 24 women; mean age 77.40 ± 10.37) fulfilled the inclusion criteria. Thirty-five eyes (51.5%) showed a PCNV, whereas the remaining 33 (48.5%) had a Type 1 CNV.

In the PCNV group (20 men and 15 women; mean age 73.14 ± 10.8 years), the mean BCVA was 83.16 ± 14.65 letters. In the Type 1 CNV group (24 men and 9 women; mean age 81.92 ± 7.77 years), the mean BCVA was 58.9 ± 18.8 letters. Patients with PCNV were younger than those with Type 1 CNV ($P = 0.0003$). Furthermore, the mean BCVA resulted to be statistically higher in the PCNV group ($P < 0.0001$). Demographic characteristics of patients with PCNV and Type 1 CNV are summarized in Table 1.

Both PCNV and Type 1 CNV eyes had previously been treated with intravitreal injections of antivascular endothelial growth factor (anti-VEGF) drugs (4.87 ± 1.03 injections vs. 6.24 ± 3.39 injections, respectively; $P = 0.09$).

SD-OCT revealed subretinal fluid in 27 of 35 PCNV eyes (77.1%), of whom 10 showed an associated hemorrhagic component. Two eyes (5.7%) presented intraretinal cysts while the remaining 6 (17.2%) showed both subretinal and intraretinal fluid.

Table 1. Demographic Characteristics (n = 68)

	PCNV	Type 1 CNV
Total eyes, n (%)		
Total patients, n (%)	35 (51.5%)	33 (48.5%)
Sex	35 (51.5%)	33 (48.5%)
Male, n (%)	20 (57.1%)	24 (40)
Female, n (%)	15 (42.9%)	9 (60)
Age, mean ± SD (years)	73.14 (10.08)	81.92 (7.77)

Categorical variables are presented as n (%).
Continuous variable is presented as mean ± SD.

In the Type 1 CNV group, 29 of 33 eyes (87.9%) showed subretinal fluid on SD-OCT, whereas 4 (12.1%) had intraretinal fluid.

By comparing the early/late ICGA frames with the OCTA images, we found that the hypercyanescent neovascular network on ICGA corresponded with the hyperreflective network on OCTA, in location and shape, both in PCNV and Type 1 CNV eyes.

To be sure of the correct location of the PCNV and Type 1 CNV, all OCTA features were matched with the multimodal imaging findings, during OCTA segmentation analysis.

The mean VPD was 0.83 ± 0.11% in PCNVs and 0.46 ± 0.10% in Type 1 CNVs ($P < 0.0001$). The mean FD was 1.44 ± 0.10 in PCNVs and 1.45 ± 0.09 in Type 1 CNVs ($P = 0.86$) while the mean LAC was 2.46 ± 1.03 in PCNVs and 1.86 ± 0.52 in Type 1 CNVs ($P = 0.006$). The results of VPD, FD, and LAC are summarized in Table 2.

Representative images of multimodal imaging, and en face OCTA angiogram with the corresponding binarized and skeletonized images of PCNV and Type 1 CNV, are shown in Figures 1 and 2, respectively.

Discussion

Although the first description of PCV dates to four decades ago,[3] whether PCNV is a separate clinical entity or a variant of Type 1 CNV is still a matter for debate in clinical retinal research.

Epidemiologic surveys have shown that PCNV occurs at an earlier age than Type 1 CNV, a finding in agreement with our results. Furthermore, the prevalence of PCNV in patients with AMD has been found to have a different geographical distribution, ranging from <10% in industrialized countries to approximately 50% in Asia.[9]

Histopathologic studies have demonstrated that the intraocular concentrations of VEGF are lower in eyes with PCNV if compared with those of nAMD eyes, suggesting that these conditions may have a different pathogenesis and disease progression.[9,19]

Table 2. Quantitative OCTA Parameters in Polypoidal Choroidal Neovascularizations and Type 1 Choroidal Neovascularizations

	PCNVs	Type 1 CNVs	*P*
VPD, mean ± SD (%)	0.83 (0.11)	0.46 (0.10)	<0.0001
FD, mean ± SD	1.44 (0.10)	1.45 (0.09)	0.86
LAC, mean ± SD	2.46 (1.03)	1.86 (0.52)	0.006

Continuous variables are presented as mean ± SD.

Important differences have been described for presentation, natural history, and prognosis. PCNV is more frequently associated with serosanguinous maculopathy or hemorrhagic pigment epithelium detachment, causing an acute, more severe vision loss than nAMD. Nevertheless, PCNV seems to have a more benign course than nAMD, which leads to a fibrovascular macular scar with consequent irreversible vision impairment.[19–21]

Furthermore, PCNV and nAMD show a different response to treatment. Indeed, PCNV is more responsive to photodynamic therapy, whereas anti-VEGF agents are more effective in nAMD.[22]

Traditional multimodal imaging has demonstrated that PCNV eyes lack drusen, the hallmark of early AMD, and showed a thicker choroid.[19] Conversely, ICGA, the gold standard for the diagnosis of PCNV and Type 1 CNV, reveals that both are characterized by a single large neovascular complex or an "ingrowth site" and draining vessels.[5]

These findings have been recently confirmed by numerous OCTA reports assessing the morphological appearance of PCNV and Type 1 CNV. According to Huang et al,[9] PCNVs are usually located centrally in the eyes with thinner choroid and present one or more main trunks of neovessels with radiating branches pointing toward the periphery of the vascular network. Similarly, Kuehlewein described Type 1 CNV as a highly organized vascular network with a main central trunk and smaller vessels radiating in a branching pattern.[23]

Overall, both ICGA and qualitative OCTA studies backed-up the theory that PCNV is a variant of Type 1 CNV because the branching vascular network of PCNV is morphologically very similar to the neovascular network of Type 1 CNV.[9,19,23]

Fractal analysis of OCTA angiograms has recently turned out to be helpful to distinguish different neovascular lesions.[11] In particular, FD, providing insight into the architecture and complexity of a vascular network, is a useful biomarker to differentiate remission Type 1 CNV from treatment-naive quiescent CNV, two different types of CNV with different natural history and prognosis.[11] Similarly, a significant difference in FD has been found between active and remission Type 1 CNVs.[24]

In our survey, PCNVs and Type 1 CNVs had an almost identical mean FD (1.44 ± 0.10 vs. 1.45 ± 0.09; $P = 0.86$). However, this FD value is lower than that reported by AL Sheik et al in a cohort of 11 patients showing active Type 1 CNV.[24] It is likely that this discrepancy may depend on the different imaging software used to estimate FD values (Image J vs. Fractalyse, respectively).[24] Overall, our results support the idea that PCNV and Type 1 CNV are characterized by

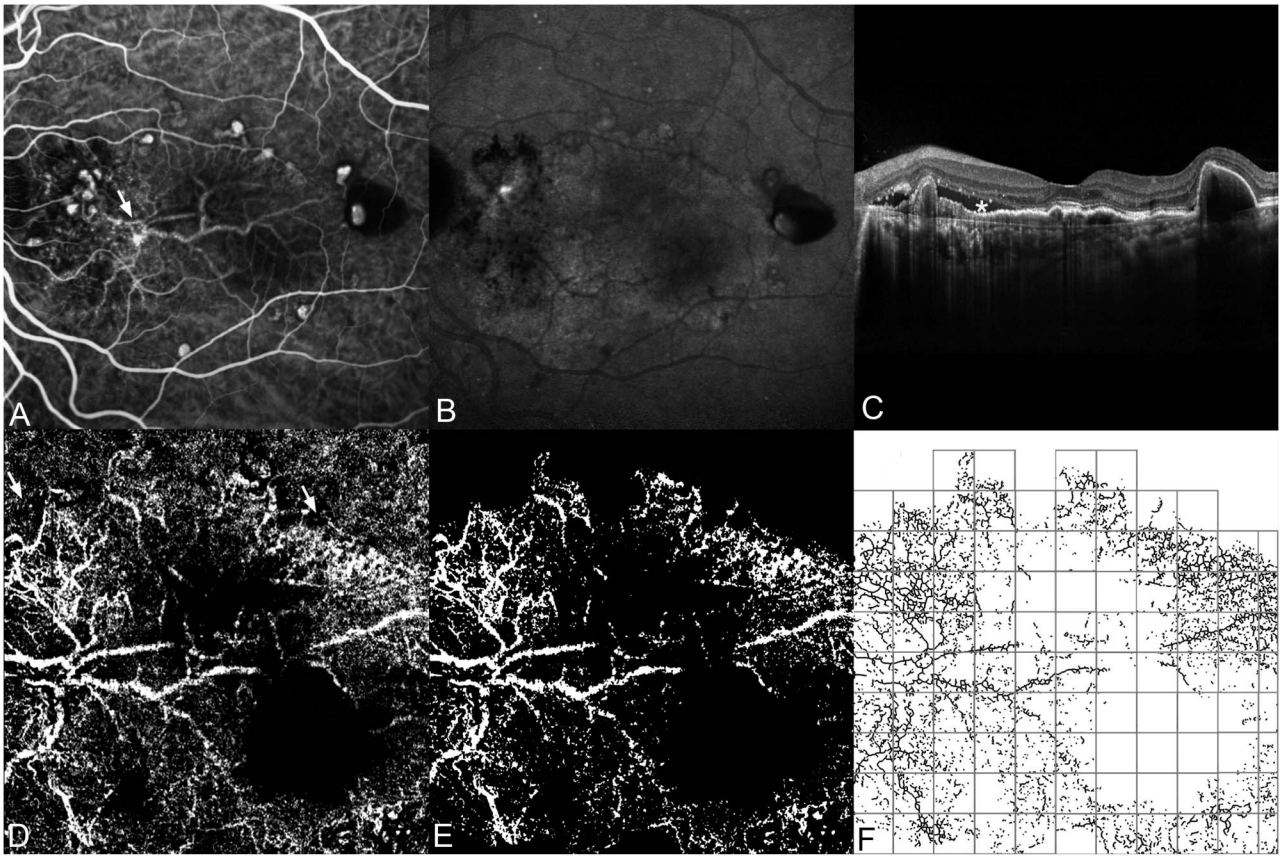

Fig. 1. Left eye: multimodal retinal imaging and optical coherence tomography angiography (OCTA) of PCNV. **A** and **B.** Early and midframe phases of indocyanine green angiography revealed a hypercyanescent vascular network corresponding to the branching vascular network with multiple aneurysmal lesions (polyps), located at the terminal ends. Note the feeder vessel of the lesion (white arrow in A). **C.** SD-OCT showing multiple peaked pigment epithelium detachments with subretinal fluid (white asterisk). **D.** The en face outer retina slab reveals the presence of a branching vascular network, appearing as a hyperreflective network with some hyporeflective aneurysmal regions suggestive of polyps (white arrows), located at the terminal ends. **E.** Binarized PCNV image obtained using the Otsu method to compute the vascular perfusion density. **F.** The box-counting method, provided by a graphical interface, was used to estimate fractal dimension and lacunarity in the skeletonized PCNV image.

the same neovascular organization and branching complexity.

Recent OCTA studies have demonstrated that the neovascular lesions may, presumably, undergo to microvascular changes secondary to the treatment with intravitreal injections of anti-VEGF drugs.[9,11] In particular, anti-VEGF drugs have been postulated to promote a vascular remodeling process characterized by pruning of small caliber capillaries as well as thickening and dilation of central prominent vessels.[11,25]

We find no statistically significant difference in the number of intravitreal injections of anti-VEGF agents between the two study groups. However, we found that PCNV eyes showed higher mean VPD values than those with Type 1 CNV, probably because the former consist of thicker vessels ending with aneurysmal dilatations,[26] whereas the latter have tiny branching vessels.[9,10]

Such anatomical differences may be the result of a hyalinization process described in PCNV lesions, which may cause the disappearance of smooth muscle actin from vessel walls and lead to vessel thickening and aneurysmal dilations.[4,27]

Future studies on treatment-naive PCNV and Type 1 CNV are necessary to elucidate this issue.

Furthermore, we found that mean LAC was significantly higher in PCNVs than in Type 1 CNVs (2.46 ± 1.03 vs. 1.86 ± 0.52, $P = 0.006$), a result suggesting that PCNVs are more heterogeneous than Type 1 CNVs. Indeed, a higher LAC translates into a greater size distribution of the lacunae, that is, a higher degree of "gappines." However, we cannot exclude that this finding may be due to the presence of shadowing artifacts on OCTA slabs. A shadowing artifact occurs when the OCTA beam is reduced or fully blocked, preventing it from reaching the underlying layers.[14,28,29]

Although the eyes with media opacities or inadequate pupillary dilations were excluded to avoid potential confounders, it is possible that the presence of extensive hemorrhagic maculopathy, observed in almost one-third of PCNV cases and completely

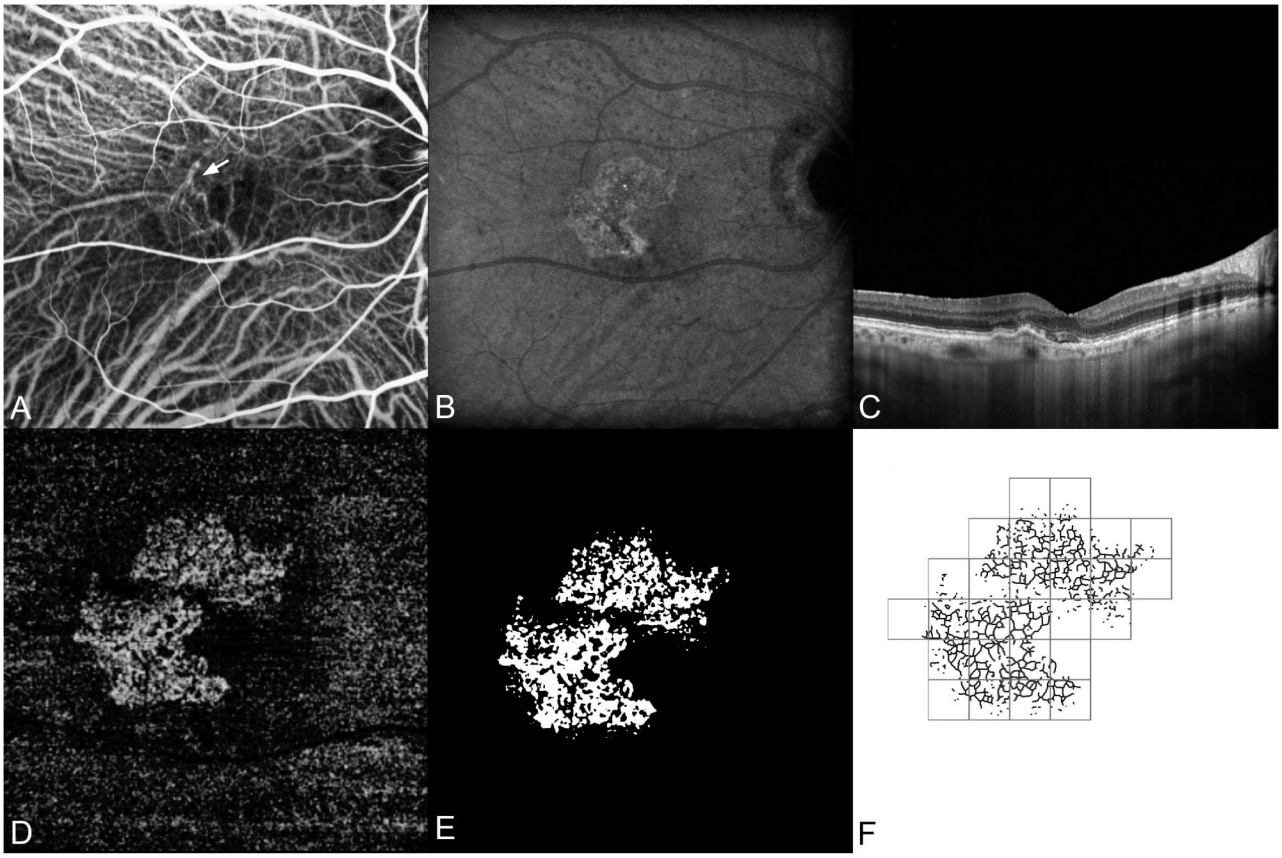

Fig. 2. Right eye: multimodal retinal imaging and optical coherence tomography angiography (OCTA) of a Type 1 choroidal neovascularization (CNV). **A.** The early phase of indocyanine green angiography reveals a hypercyanescent neovascular network, which appears as a hypercyanescent plaque in the late phase (**B**). Note the feeder vessel of the lesion (white arrow in A). **C.** SD-OCT showing a subfoveal vascularized pigment epithelium detachment with subretinal fluid. **D.** En face outer retina OCTA slab revealing a hyperreflective network suggestive of Type 1 CNV. **E.** Binarized Type 1 CNV image obtained using the Otsu method to compute the vascular perfusion density. **F.** The box-counting method, provided by a graphical interface, was used to estimate fractal dimension and lacunarity in the skeletonized Type 1 CNV image.

absent in the Type 1 CNV group, may have affected LAC results.

We are aware that our survey presents some limitations, including the retrospective nature of the study and the relatively small numbers of examined eyes. Furthermore, all study eyes were previously treated with intravitreal injections of anti-VEGF drugs. A prospective study consisting of patients with treatment-naive neovascular lesions should be performed to definitively establish whether PCNV and Type 1 CNV are different clinical entities. Finally, the presence of a large hemorrhagic maculopathy, frequently detected in active PCNV eyes, could have somehow affected our results obtained by the application of the fractal analysis.

Nonetheless, to the best of our knowledge, this is the first study comparing OCTA fractal analysis results from AMD eyes with PCNV and Type 1 CNV.

In conclusion, our study revealed that patients with PCNV were younger and with a higher mean BCVA than those with Type 1 CNV. Fractal analysis disclosed that PCNVs and Type 1 CNVs have similar neovascular architecture and branching complexity, but PCNVs were more heterogeneous and characterized by higher VPD and LAC values than Type 1 CNVs. These interesting findings seem to support the idea that PCNVs and Type 1 CNVs are two separate clinical entities. However, future studies based on OCTA fractal analysis, but also involving other relevant parameters such as demographics, presentation, morphology on multimodal imaging, and response to treatment, are necessary before drawing any definitive conclusions on whether PCNV is a specific clinical entity or a nAMD variant.

Key words: age-related macular degeneration, fractal dimension, lacunarity, optical coherence tomography

angiography, polypoidal choroidal neovascularization, Type 1 choroidal neovascularization.

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