Nonexudative Perifoveal Vascular Anomalous Complex: The Subclinical Stage of Perifoveal Exudative Vascular Anomalous Complex?

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• PURPOSE: To describe the pre-exudative stage of exudative perifoveal vascular anomalous complex (ePVAC), referred to as nonexudative PVAC (nePVAC).

• DESIGN: Retrospective noncomparative case series.

• METHODS: Patients diagnosed with nePVAC were identified at 4 retina referral centers worldwide. Multimodal retinal imaging, including structural optical coherence tomography (OCT) and OCT-angiography (OCT-A), were performed at baseline and follow-up visits.

• RESULTS: Six eyes (6 patients, mean 75 ± 10 years of age) were included. Unrelated chorioretinal diseases were diagnosed in the affected eyes in 5 of 6 cases. At baseline, nePVAC is characterized by microvascular abnormalities featuring an isolated, perifoveal, large intraretinal aneurysm surrounded by capillary rarefaction at OCT-A examination, without any sign of exudation with structural OCT, and without visual impairment. Four patients were followed for a mean of 21 ± 14 months. During the follow-up, 3 of 4 eyes (75%) developed signs of exudation after a mean of 15 ± 9 months, associated with metamorphopsia and visual decline at the time of exudation. Best-corrected visual acuity decreased from 20/25 to 20/40 Snellen equivalent ($P = .035$) and central macular thickness increased from 268 ± 27 μm to 339 ± 65 μm ($P = .145$). Three patients were treated with 2.3 ± 0.6 intravitreal injections of anti–vascular endothelial growth factor without significant improvement of best-corrected visual acuity or macular edema.

• CONCLUSIONS: nePVAC may represent the subclinical pre-exudative stage of ePVAC, notable for an absence of exudation or visual impairment. nePVAC and ePVAC should be considered as part of the same spectrum, namely PVAC. Typically, nePVAC develops signs of exudation over time, causing metamorphopsia and visual decline and therefore these lesions warrant continued close monitoring with multimodal retinal imaging. (Am J Ophthalmol 2020;218:59–67. © 2020 Elsevier Inc. All rights reserved.)

PERIFOVEAL EXUDATIVE VASCULAR ANOMALOUS complex (PEVAC) is a relatively new entity described for the first time in 2011 by Querques and associates[1] as a unilateral, isolated, perifoveal aneurysmal lesion surrounded by focal microvascular abnormalities. As reported by our group and others,[1–8] PEVAC is a macular disease that can affect healthy patients but also patients with other coincident macular diseases, including age-related macular degeneration (AMD) and pathologic myopia. With multimodal imaging, PEVAC appears as an isolated aneurysmal lesion with detectable internal flow using optical coherence tomography angiography (OCTA).[1–4] Using structural OCT, PEVAC is usually located in the retinal layers between the outer plexiform layer (OPL) and the ganglion cell complex (GCC), displaying signs of exudation.[1–4] The intraretinal cystoid macular edema caused by PEVAC is usually unresponsive to intravitreal injections of anti–vascular endothelial growth factor (VEGF),[1,2,4] even if a patient with PEVAC had complete resolution of the exudation after 13 intravitreal anti-VEGF injections as reported by Mrejen and associates.[3] Thermal laser photocoagulation has been associated with better results with resolution of the intraretinal cystoid edema, but laser also has risks because of the proximity of PEVAC to the fovea.[3] Typically, PEVAC lesions show a stable clinical course, with no significant improvement or worsening in the visual function and intraretinal cystoid macular edema during follow-up.[1–3] However, in some cases, spontaneous resolution of the intraretinal edema may occur.[1,4]

Recently, several authors have expanded our knowledge regarding the multimodal retinal imaging features of PEVAC.[2–8] However, studies to detect evidence of PEVAC preceding the onset of exudation are lacking.

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The purpose of the present study was to describe nonexudative perifoveal vascular anomalous complex (nePVAC), which may represent a subclinical preexudative stage of PEVAC, characterized by focal microvascular abnormalities and an isolated aneurysmal lesion but without signs of exudation. Assuming the latter, we propose to slightly change the original acronym for the exudative lesion from PEVAC to ePVAC (exudative perifoveal vascular anomalous complex). By keeping the same pronunciation, all the spectrum is named the same, which in turn allows better categorizing of the exudative and nonexudative form of PVAC. We report on the multimodal imaging findings and the clinical progression of nePVAC.

METHODS

THIS WAS A RETROSPECTIVE NONCOMPARATIVE CASE SEries comprised of 4 retina referral centers (Medical Retina and Imaging Unit of the Department of Ophthalmology of University Vita-Salute San Raffaele in Milan, Italy; Vitreous Retina Macula Consultants of New York, in New York, New York, USA; Department of Ophthalmology of University Paris Est, in Creteil, France; and the Doheny Eye Institute, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California, USA). Clinical data of nePVAC cases presenting between September 2014 and September 2019 were collected. The study was conducted in accordance with the tenets set forth in the Declaration of Helsinki for research involving human subjects. All patients signed a written informed consent and respective local institutional review board or ethics committee approval was obtained by the coauthors of this study for each of all 4 involved centers.

The inclusion criteria for this study included patients ≥18 years of age with a diagnosis of nePVAC. nePVAC was defined as an isolated, perifoveal, large retinal aneurysm surrounded by microvascular abnormalities, and without any sign of exudation (ie, no evidence of intraretinal or subretinal fluid by spectral-domain OCT) at the baseline visit.

Exclusion criteria included: 1) the presence of diabetes mellitus, uncontrolled hypertension, or other systemic cardiovascular diseases; 2) the presence of any other retinal vascular diseases (eg, diabetic retinopathy, retinal vein occlusion, retinal artery occlusion, or hypertensive retinopathy); 3) presence of any inflammatory retinal diseases (ie, posterior uveitis); 4) any previous retinal treatments (eg, laser photocoagulation, photodynamic therapy, intravitreal injections of anti-VEGF or steroid); 5) presence of significant media opacities limiting the quality of multimodal imaging (eg, corneal opacity or cataract or anterior or vitreous cellular reaction).

Clinical charts were retrospectively reviewed and demographic information, medical history, and history of previous retinal treatments were recorded. As part of the standard clinical assessment, enrolled patients underwent clinical examination, including best-corrected visual acuity (BCVA), and multimodal imaging evaluation including color fundus photography or MultiColor imaging, near infrared reflectance (NIR), short-wave fundus autofluorescence (FAF), structural spectral-domain OCT, and OCTA. MultiColor imaging, NIR, and FAF were performed using the Spectralis HRA + OCT (Heidelberg Engineering, Heidelberg, Germany). Structural OCT examinations were performed using the Spectralis HRA + OCT or Cirrus 5000 (Zeiss Meditech, Inc, Dublin, California, USA). Central macular thickness (CMT) was measured with the OCT volume scan and using the automated built-in software in the central 1-mm–diameter circle of the ETDRS thickness map. OCTA examinations were performed using the 3-mm × 3-mm en face image centered on the lesion (PlexElite 9000 Swept-Source OCT-A, Zeiss Meditech, Inc, or AngioVue RTVue XR Avanti, Optovue, Fremont, California, USA). All images were analyzed by a senior retinal specialist that manually adjusted all segmentation slabs provided by the OCTA software for optimal visualization of the retinal plexuses and choriocapillaris.

Relevant clinical findings available at baseline and at all follow-up examination visits were reviewed and retrospectively analyzed by 2 trained examiners (RS, EB).

• **STATISTICAL ANALYSIS:** Statistical analyses were performed using SPSS software (v 20; IBM Corp, Armonk, NY, USA). In all patients, BCVA was converted to logarithm of the minimum angle of resolution (LogMAR) for statistical analysis. All values of descriptive analyses were expressed as counts and percentages for categorical variables, and as means ± standard deviations for quantitative variables. The paired student *t* test was used to compare BCVA and CMT between the baseline and the final follow-up, after verification of the Gaussian distribution with the Kolmogorov-Smirnov test.

$P < .05$ was considered statistically significant in all analyses.

RESULTS

SIX EYES OF 6 WHITE PATIENTS FULFILLED THE INCLUSION criteria and were included in the current study. One patient was included from the Department of Ophthalmology of University Vita-Salute San Raffaele, 3 from the Vitreous Retina Macula Consultants of New York, 1 from the Department of Ophthalmology of University Paris Est, and 1 from the Doheny Eye Centers in Los Angeles. The mean age of the cohort was 75 ± 10 years (median 75.5

TABLE. Demographic Characteristics, Clinical Findings, and Multimodal Imaging Features of Patients With Nonexudative Perifoveal Vascular Anomalous Complex, the Potential Pre-exudative Stage of Exudative Perifoveal Vascular Anomalous Complex, Including Recorded Changes at the Exudative Stage

Patient No.	Sex/Age, y	Eye of Lesion	Coincident Eye Disease	BCVA Pre-exudative Stage(Snellen)	CMT Pre-exudative Stage (μm)	Intraretinal Location of nePVAC at Structural OCT	OCTA Retinal Plexus Localization	Total Follow-Up (Months)	Exudation	Time to Exudation (Months)	Final BCVA (Snellen)	Final CMT (μm)
1	M/60	OS	None	20/20	218	ONL, OPL, INL, and IPL	SCP and DVC	N/A	—	—	—	—
2	M/88	OD	i-AMD	20/32	296	ONL, OPL, and INL	SCP and DVC	7	YES	5	20/63	421
3	M/72	OD	i-AMD and myopia	20/25	277	OPL, INL, and IPL	SCP and DVC	11	NO	—	20/32	274
4	F/80	OS	i-AMD	20/32	281	OPL, INL, and IPL	SCP and DVC	36	YES	24	20/40	302
5	M/79	OS	i-AMD	20/20	268	ONL, OPL, INL, and IPL	SCP and DVC	30	YES	20	20/32	358
6	F/72	OS	Pachychoroid	20/25	270	IPL and GCC	SCP	N/A	—	—	—	—

BCVA = best-corrected visual acuity; CMT = central macular thickness; DVC = deep vascular complex; F = female; GCC = ganglion cell complex; i-AMD = intermediate age-related macular degeneration; INL = inner nuclear layer; IPL = inner plexiform layer; M = male; N/A = not available; nePVAC = nonexudative perifoveal vascular anomalous complex; OCT = optical coherence tomography; OCTA = optical coherence tomography angiography; OD = right eye; ONL = outer nuclear layer; OPL = outer plexiform layer; OS = left eye; SCP = superficial capillary plexus; y = years.

years; range 60-88 years) and 2 patients were female and 4 were male. None of the patients endorsed a history of diabetes or other vascular diseases, although 2 patients reported a history of medically controlled essential hypertension.

At the time of nePVAC diagnosis, the mean BCVA was 20/25 Snellen equivalent (0.10 ± 0.09 logMAR; median, 0.10; range 0-0.2) and the mean CMT was 268 ± 27 μm (median, 273.5; range 218-296 μm). At baseline, none of the patients had evidence of decreased vision because of the presence of a nePVAC lesion (Table). Of note, all patients displayed evidence of other coincident chorioretinal diseases affecting the study or the fellow eye. Specifically, 3 of 6 patients (50%) were diagnosed with intermediate AMD, 1 of 6 patients (16.7%) with both myopia and intermediate AMD, 1 of 6 patients (16.7%) with pachychoroid disease, and 1 of 6 patients (16.7%) with an epiretinal membrane in the fellow eye (the study eye was unremarkable except for the nePVAC lesion; Table).

The diagnosis of nePVAC was based on fundus examination and multimodal imaging evaluation. Specifically, nePVAC appeared as an isolated aneurysmal lesion, located in the perifoveal region, with no signs of exudation (ie, no evidence of hard exudates or intraretinal or subretinal fluid; Figure 1). Using structural OCT, nePVAC exhibited features of a large microaneurysm, with a round hyperreflective wall that surrounded a lumen containing variably reflective material (Figure 1). The lesion was variably located between the outer nuclear layer and the GCC layer (Table). None of the lesions displayed any evidence of choroidal neovascularization extension into the subretinal pigment epithelium (sub-RPE).

OCTA was performed using AngioVue in 5 patients and PlexElite 9000 in 1 patient. OCTA showed an isolated large dilated aneurysm corresponding to the nePVAC lesion with detectable flow in both the superficial capillary plexus and the deep vascular complex (DVC) (5 cases), or involving only the superficial capillary plexus (1 case; Table). Furthermore, in all 6 cases, there was evidence of retinal microvascular abnormalities in the form of rarefaction of the surrounding retinal capillaries and a shadow effect in the choriocapillaris caused by the large aneurysm (Figure 2). No other concomitant vascular abnormalities were disclosed in the retinal vascular plexuses of the choriocapillaris.

Four of 6 patients (67%) were followed for a mean of 21 ± 14 months (median, 20.5; range 7-36 months; Figures 3 and 4). Two patients were lost during follow-up. During follow-up, 75% (3 of 4 cases) developed signs of exudation after a mean of 15 ± 9 months. Patients typically complained of metamorphopsia with a slight visual decline at the time of exudation. BCVA significantly declined to approximately 20/40 Snellen equivalent (0.30 ± 0.14 logMAR; median, 0.25; range, 0.2-0.5 LogMAR; P = .035) and mean CMT increased to 339 ± 65 μm (median, 330 μm; range, 274-421 μm; P = .145; Table). On fundus

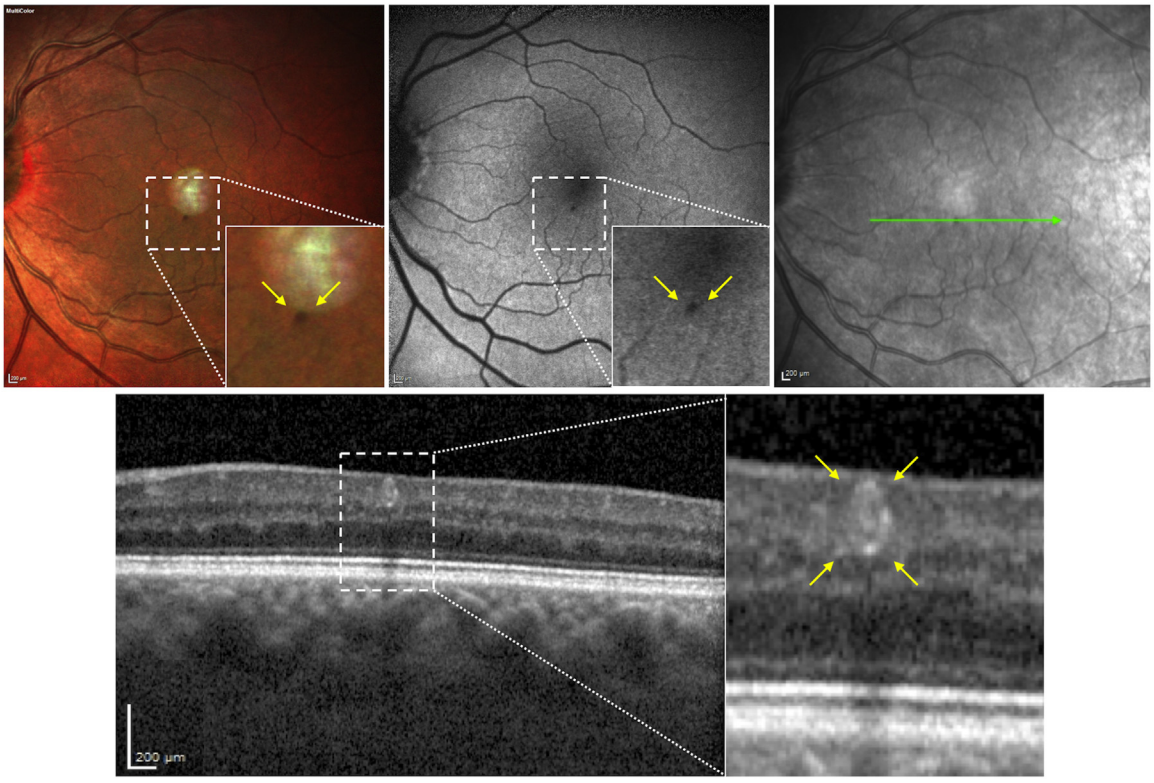

FIGURE 1. Multimodal imaging evaluation of patient 6 with nonexudative perifoveal vascular anomalous complex in the left eye at the nonexudative baseline stage. (Top row) Multicolor imaging (left panel), fundus autofluorescence (middle panel), and near infrared reflectance (right panel) show a perifoveal isolated aneurysmal lesion, without any other retinal abnormalities. (Right panel) The green arrow denotes the level of segmentation of the optical coherence tomography B-scan (second row). (Bottom row) Optical coherence tomography B-scan passing through the nonexudative perifoveal vascular anomalous complex lesion shows a round lesion with a hyperreflective wall (yellow arrows), without associated intraretinal cystic fluid.

examination, 2 of 3 eyes showing exudation (67% of cases) presented with hard exudates. By means of structural OCT, intraretinal cystic spaces were detected in all 3 exudative cases (Figure 3). All 3 exudative cases were treated with a mean of 2.3 ± 0.6 intravitreal injections of anti-VEGF (either aflibercept or ranibizumab) without improvement of BCVA (final BCVA of approximately 20/40 Snellen equivalent, 0.28 ± 0.10 logMAR; median, 0.25; range, 0.2-0.4 logMAR) and with no evidence of resolution of intraretinal cystic spaces.

DISCUSSION

IN THIS STUDY, WE HAVE DESCRIBED A NOVEL LESION THAT may represent a subclinical pre-exudative stage of PEVAC, which we propose renaming nePVAC. Importantly, if we have demonstrated the presence of a nonexudative stage, we also proposed to rename the exudative lesion previously known as PEVAC as ePVAC. The latter slight change allows to better distinguish the nonexudative and exudative forms and it reduces possible confusion in distinguishing these 2 lesions.

At baseline, nePVAC lesions displayed all the features of ePVAC but without signs of exudation or associated visual impairment. However, nePVAC lesions ultimately exhibited evidence of exudation in 75% of cases after a mean of 15 ± 9 months follow-up from the baseline examination, eventually fulfilling all criteria of ePVAC lesions. For these reasons, we propose that these 2 entities (ePVAC and nePVAC) should be considered part of the same entity, namely PVAC, that could be associated with or without exudation (ePVAC and nePVAC, respectively).

Exudative PVAC is a retinal capillary abnormality first described as PEVAC by Querques and associates[1] in 2011 as an isolated, unilateral, perifoveal aneurysmal lesion. Our group expanded the spectrum of this entity reporting the multimodal imaging and clinical features.[2] Of note, patients with ePVAC typically complain of visual decline and metamorphopsia caused by intraretinal exudation associated with the aneurysmal lesion. The nature of exudation is usually self-limited, without evidence of progression or visual decline.[2,4] Furthermore, intraretinal exudation associated with ePVAC may not respond to anti-VEGF treatment, and, rarely, the exudation can spontaneously regress which may be related to variability of the flow inside

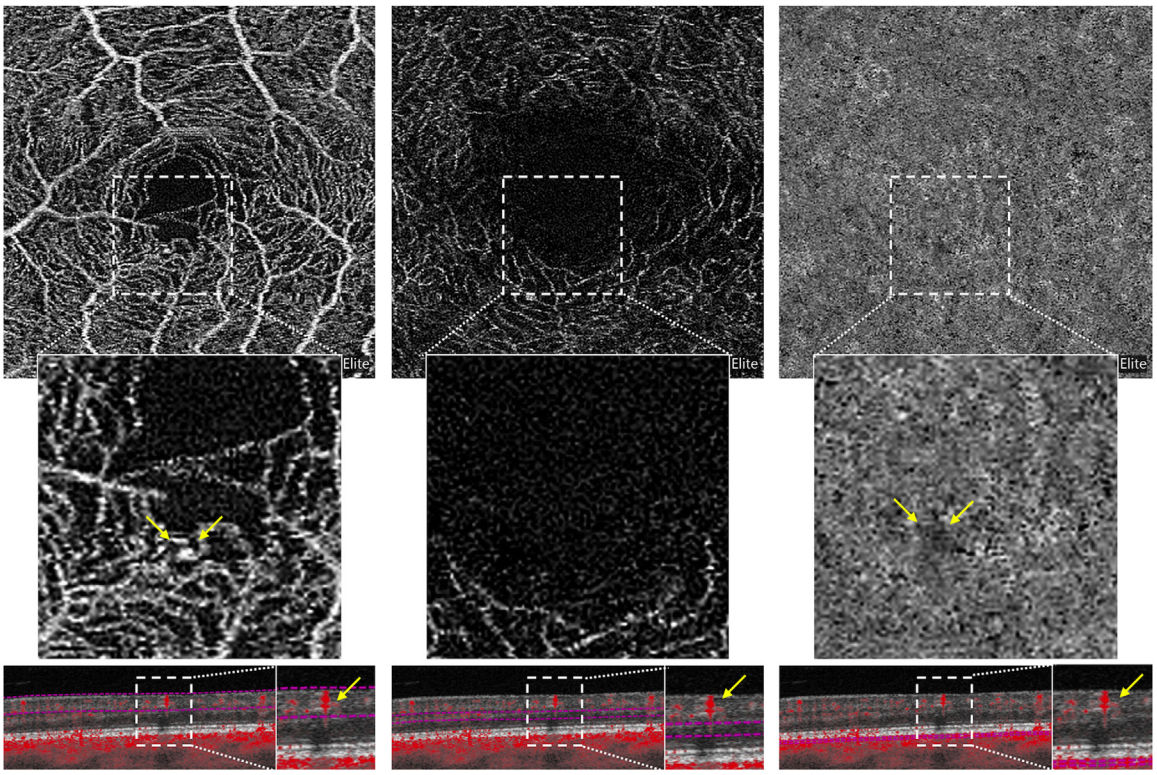

FIGURE 2. Optical coherence tomography angiography of patient 6 with nonexudative perifoveal vascular anomalous complex in the left eye at the nonexudative baseline stage. Three millimeter by 3-mm en face optical coherence tomography angiography images and corresponding B-scans with flow overlay show an isolated large dilated lesion (yellow arrows) corresponding to nonexudative perifoveal vascular anomalous complex with detectable flow in the superficial capillary plexus (left panel) and no flow in the deep vascular complex (middle panel). The lesion is characterized by rarefaction of retinal capillaries in the perilesional area of the superficial capillary plexus (first panel) and a shadowing artifact in the choriocapillaris (right panel).

the aneurysmal lesion.[2–4] In the previously published series about ePVAC, the aneurysmal lesion was identified in healthy subjects or in patients with other concomitant macular diseases (mainly AMD and myopia), except other ocular vasculopathy for definition.[2–4] We reported that nePVAC lesions are also associated with the same macular diseases, strengthening the hypothesis that ePVAC and nePVAC could be part of the same spectrum of disease. Because the mean age of patients affected by PVAC, the spread variability of the macular diseases and their nonvascular nature, we consider these associations as coincidental.

We reported a possible pre-exudative stage of PVAC. These lesions fulfilled all diagnostic criteria of ePVAC, except for the presence of exudative features (Figure 1). In a previous series, Mrejen and associates[3] reported a case of ePVAC in which a FA performed 4 years before the inclusion showed that the PVAC lesion was present at that time but without significant exudation. For this reason, probably, also that case could represent a nePVAC lesion. Because of the absence of exudation, nePVAC lesions are asymptomatic in the initial stage, without visual decline or other visual symptoms related to the disease. Because of the high percentage of exudation (Figure 3) associated with visual decline (75% of cases in our series), we recommend careful monitoring of nePVAC for the early identification of exudative signs that may warrant therapeutic intervention.

Although 75% of cases in our series developed exudation during follow-up, 1 case did not (Figure 4). Moreover, we cannot exclude the possibility that nePVAC may even resolve without any evidence of progression to ePVAC, possibly the result of thrombosis of the aneurysmal lesion. Luminal occlusion of other micro- and macroaneurysms has been reported in the literature in other retinal diseases.[9,10] With OCTA, nePVAC appears as an aneurysmal lesion with detectable internal flow (Figure 2). The flow inside the lesion can change during the follow-up. Increased flow with OCTA may indicate the development of exudative complications and progression of the lesion from the subclinical pre-exudative (ie, nePVAC) to the exudative stage while closure of the nePVAC lesion may signal resolution of the process. The pathogenesis of the disease remains unclear; however, focal endothelial cell injury has been proposed as the basis of the disease.[2] Reduction of pericyte protection of endothelial cells

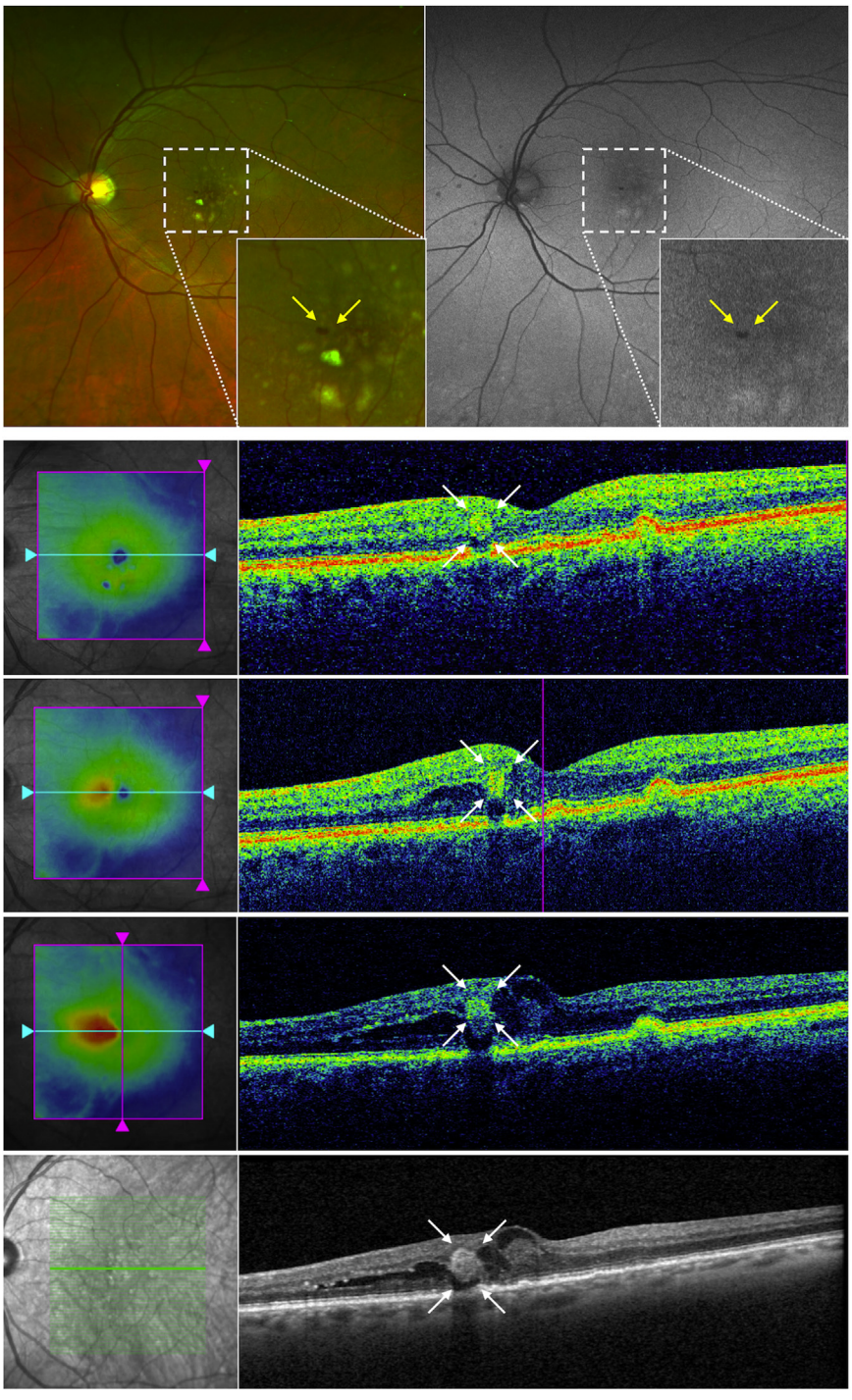

FIGURE 3. Multimodal imaging evaluation of patient 5 with nonexudative perifoveal vascular anomalous complex (nePVAC) in the left eye at the pre-exudative stage (ie, baseline) and at follow-up examinations. (Row 1) Multicolor imaging (left panel) and fundus autofluorescence (right panel) show a perifoveal isolated aneurysmal lesion corresponding to nePVAC (yellow arrows) with associated macular drusen, an unrelated finding. (Rows 2-5) Combined infrared reflectance imaging and structural optical coherence tomography at baseline (ie, pre-exudative stage) (second row), 20-month follow-up (evidence of exudation) (third row), 26-month follow-up (before intravitreal injections of anti–vascular endothelial growth factor [VEGF]) (fourth row), and 30-month follow-up (1 month after 3 intravitreal injections of anti-VEGF) (fifth row) show the progression of the nePVAC lesion (white arrows). Of note, the nePVAC lesion with exudation (corresponding to the perifoveal exudative vascular anomalous complex stage) shows no response to the intravitreal injections of anti-VEGF (fourth and fifth rows) and it is isolated in the retinal layers with no signs of extension to the retinal pigment epithelium (RPE)/sub-RPE space.

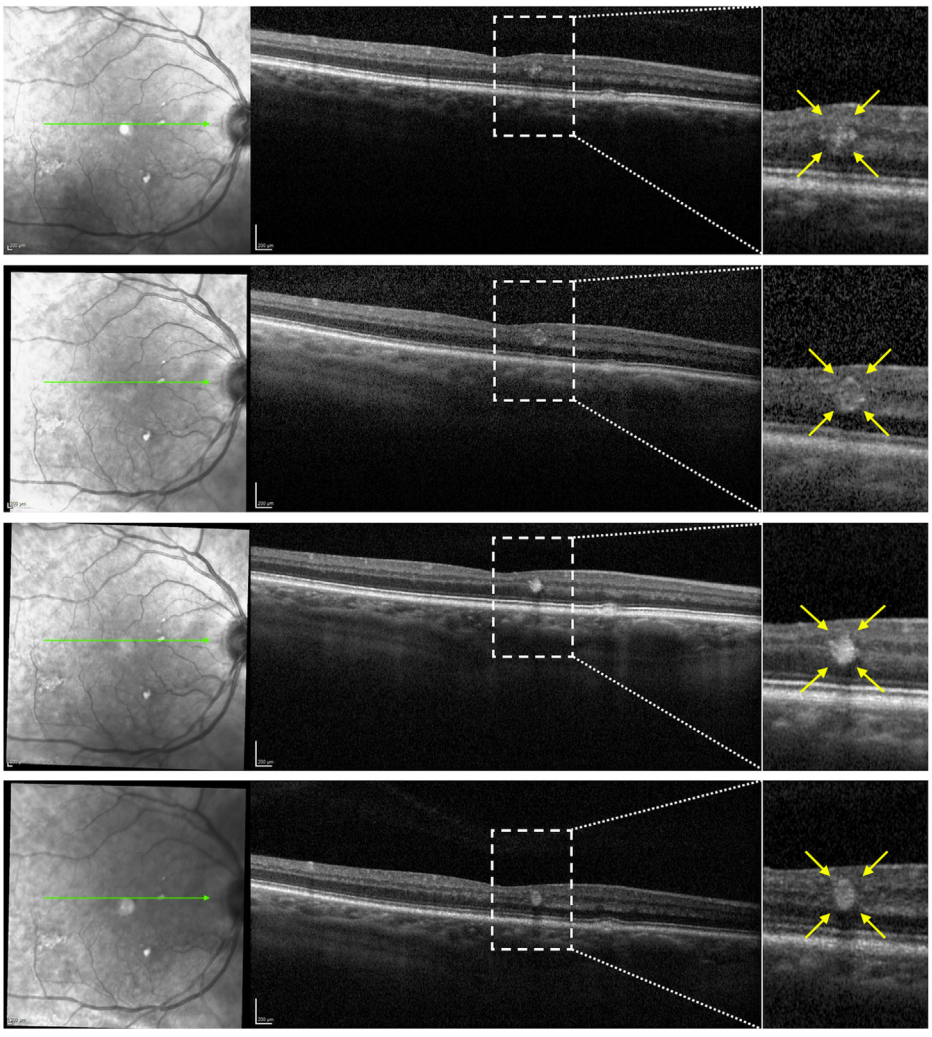

FIGURE 4. Horizontal structural optical coherence tomography B-scans at the level of the nonexudative perifoveal vascular anomalous complex (nePVAC) lesion in patient 3 at the pre-exudative stage (ie, baseline) and at all follow-up visits. Combined infrared reflectance imaging and structural optical coherence tomography at baseline (first row), 1-month (second row), 6-month (third row), and 11-month (fourth row) follow-up visits show the progression of the nonexudative perifoveal vascular anomalous complex lesion (yellow arrows) which displays a round hyperreflective wall without any evidence of associated exudation at any of the follow up visits.

because of breakdown of the basement membrane has been postulated to explain the larger isolated aneurysms.[11] Increased endothelial damage may therefore lead to exudation and progression of nePVAC (a subclinical nonexudative stage) to ePVAC.

The differential diagnosis of PVAC spectrum is essential in the management of this disease. Recently, the introduction of the multimodal imaging approach (especially OCTA) into clinical practice has provided a better understanding of the diagnosis of different retinal diseases.[12–16] PVAC lesions should be differentiated mainly from macroaneurysms/large microaneurysm, type 1 macular telangiectasia (MacTel), and nascent type 3 lesions.[17–21] Macroaneurysms and large microaneurysms are usually caused by other retinal vascular disorders, such as retinal vein occlusion, diabetic retinopathy, and inflammatory diseases.[17,18] For this reason, we excluded patients with any systemic vascular disease (ie, uncontrolled arterial hypertension, diabetes, and other vascular diseases) in our series. In addition, PVAC displayed evidence of retinal microvascular abnormalities (rarefaction of the surrounding retinal capillaries) that is not present in case of macroaneurysm or isolated large microaneurysm.[17,18] The capillary rarefaction around the PVAC lesions was already reported by our group[2] and by Mrejen and associates[3] in the exudative stage (ie, ePVAC). As this OCTA feature has been confirmed also in the nonexudative form of PVAC, the capillary rarefaction could be considered as hallmark of the PVAC spectrum.

Type 1 MacTel is characterized by cystoid macular edema due to a more widespread intraretinal microangiopathy in young males.[21] On the other hand, PVAC is characterized by an isolated perifoveal aneurysmal abnormality showing attenuation of the retinal capillaries around the lesion but without other capillary aneurysms or telangiectatic changes. Furthermore, PVAC typically affects older patients in comparison to type 1 MacTel. Differentiation from nascent type 3 macular neovascularization can be challenging, especially with respect to nePVAC (the subclinical nonexudative stage of ePVAC). Nascent type 3 macular neovascularization is characterized by intraretinal hyperreflective foci with detectable flow using OCTA in the DVC, without any evidence of exudation or with mild microcystic change until the lesion progresses to involve the RPE and sub-RPE space.[21] Indeed, nascent type 3 macular neovascularization typically displays evidence of downgrowth progression from the DVC to the RPE and sub-RPE space, which may be essential for the exudative process.[21] On the other hand, nePVAC lesions are located in the retinal layers, showing no progression to the RPE and sub-RPE space. Furthermore, their morphology on structural OCT is different from nascent type 3 macular neovascularization. In both exudative and nonexudative forms of PVAC, the aneurysmal lesions are characterized by a round hyperreflective wall surrounding a lumen containing variably reflective material, while nascent type 3 macular neovascularization is characterized by a hyperreflective focus without a detectable lumen inside.[21] More advanced type 3 lesions may show evidence of downward subsidence of the outer plexiform layer that can be another distinguishing feature.[22,23]

We acknowledge that there are several limitations in this study, mainly because of the relatively small sample size and the retrospective nature of the study. However, nePVAC are relatively rare diseases, and, in this series, our inclusion criteria were strict and selective.

In conclusion, PVAC is an isolated, perifoveal, aneurysmal lesion, surrounded by focal microvascular abnormalities, occurring in otherwise healthy patients with or without other concomitant macular diseases. nePVAC may represent the subclinical pre-exudative stage of ePVAC (previously named as PEVAC), notable for an absence of exudation or visual impairment. For this reason, nePVAC and ePVAC should be considered part of the same spectrum of the disease, namely PVAC. nePVAC lesions may develop signs of exudation in most cases during follow-up, leading to metamorphopsia and visual decline and possibly necessitating interventional treatment, and therefore continued follow-up with multimodal imaging is recommended.

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