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Optical Coherence Tomography Angiography in Eyes with Indeterminate Choroidal Neovascularization: Results from the AVATAR study

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Abstract

Objective: To evaluate the use of optical coherence tomography angiography (OCTA) to detect choroidal neovascularization (CNV) in eyes with indeterminate CNV features on conventional imaging.

Design: The AVATAR study is a prospective observational study of OCTA in patients undergoing routine spectral-domain optical coherence tomography (SD-OCT) for macular disease.

Participants: Subjects enrolled in the AVATAR study for which CNV was considered as part of a differential diagnosis based on clinical exam and/or prior imaging, but in whom the presence of CNV was not definitive on SD-OCT and fluorescein angiography (FA) imaging.

Interventions: All patients were imaged with the Avanti RTVue XR HD (Optovue, Fremont, CA) and the Cirrus HD-OCT (Zeiss, Oberkochen, Germany) systems.

Main Outcome Measures: OCTA scans were assessed for the presence or absence of CNV. SD-OCT scans were assessed for the presence of fluid, hyperreflective material, serous pigment epithelial detachment (PED), shallow irregular PED, vitreomacular adhesion, epiretinal membrane, retinal pigment epithelium atrophy and central subfield retinal thickness. Univariate and multivariate logistic regression analyses were performed to identify features on SD-OCT associated with the presence of CNV on OCTA.

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Results: Twenty-nine eyes of 29 patients met the criteria for inclusion. A CNV lesion was detected on OCTA in 8 (28%) eyes; 21 (72%) eyes were negative for CNV. After adjusted for age, gender and central subfield retinal thickness, the presence of shallow irregular PED [odds ratio, 148; 95% confidence interval, 3.22–6830; $p = 0.011$], as well as the combinations of intraretinal fluid and sub-retinal pigment epithelium material [odds ratio, 16.8; 95% confidence interval, 1.43–198; $p = 0.025$] on SD-OCT were significantly associated with the presence of CNV on OCTA.

Conclusions: OCTA enabled the identification of CNV that was otherwise indeterminate with prior imaging in select eyes. The presence of a shallow irregular PED as well as intraretinal fluid combined with sub-retinal pigment epithelium material were both associated with the presence of CNV. OCTA may be a valuable adjunct to conventional SD-OCT and FA imaging in the detection and surveillance of CNV, particularly in diagnostic dilemmas.

Introduction

Choroidal neovascularization (CNV) is a relatively common complication of a number of retinal diseases including age-related macular degeneration (AMD), ocular histoplasmosis, myopia and chronic central serous chorioretinopathy (CSCR).^{1–3} Early detection and surveillance of active exudation from CNV is essential to the prevention of poor visual outcomes.⁴

Current imaging technologies have transformed clinicians' ability to detect subtle signs of exudation and potential underlying CNV. Many would argue that the gold standard for diagnosing CNV is fluorescein angiography (FA), a technique that allows for the dynamic evaluation of leakage from classic and occult membranes.⁵ FA, however, has a number of drawbacks. It is an invasive test that requires the intravenous injection of sodium fluorescein. Although it is typically well tolerated, a small number of patients may experience side effects such as nausea, vomiting, or even severe allergic reactions.⁶ In addition, obtaining high-quality FA images requires a highly skilled photographer or support personnel; many satellite offices may not have such capabilities. Finally, the results of FA may be difficult to interpret in cases of indeterminate leakage or staining in an area of interest without definitive signs of CNV. Such situations may present a diagnostic challenge to clinicians.

Spectral-domain optical coherence tomography (SD-OCT) is a non-invasive imaging technology that generates high-resolution cross-sectional scans of the retina. It allows for the visualization of structural changes, such as fluid accumulation or pigment epithelial detachment (PED), that suggest active exudation from a CNV lesion.⁷ In recent years, SD-OCT has emerged as not only the imaging modality of choice for ongoing monitoring of active exudation from CNV lesions, but also as the most frequently utilized test for the initial diagnosis of many retinal conditions associated with CNV such as neovascular AMD.⁸ Despite its utility in the detection of active exudation, the ability of SD-OCT to definitively identify CNV is unknown. The presentation of CNV on SD-OCT overlaps with those of other simulating conditions such as non-neovascular AMD with macular edema from other causes or degenerative cystic changes.⁹ While CNV tissue can sometimes be visualized directly as hyperreflective material below the retina or retinal pigment epithelium (RPE), definitive identification is often difficult due to the similar location and reflectivities of CNV,

drusenoid deposits, vitelliform material, hemorrhage, and thick fibrin as well as the RPE and the choroid.¹⁰ In patients with indeterminate FA findings, it may be difficult for clinicians to clearly establish or rule out the presence of CNV on the basis of SD-OCT alone.

Optical coherence tomography angiography (OCTA) is an emerging imaging modality that allows for noninvasive, direct visualization of blood flow within retinal and choroidal vessels.¹¹ In spectral-domain OCTA, split-spectrum amplitude-decorrelation (SSADA) software detects motion contrast between blood flow and surrounding static tissue to generate a volumetric angiogram.¹¹ Prior studies have shown that OCTA is capable of visualizing CNV in a variety of macular diseases including neovascular AMD, chronic CSCR and myopic degeneration.^{12–14} OCTA may be a useful tool to help facilitate the identification of CNV in patients with indeterminate findings on conventional imaging techniques.

In this study, we evaluate the ability of OCTA to visualize CNV in patients with suspected but indeterminate CNV on standard diagnostic imaging. In addition, we analyze the features on SD-OCT that are most strongly linked to the presence of CNV on OCTA.

Methods

The Observational Assessment of Visualizing and Analyzing Vessels with Optical Coherence Tomography Angiography in Retinal Diseases (i.e., **AVATAR** Study) is a prospective observational study examining OCTA in eyes undergoing routine SD-OCT for the macular disease at the Cole Eye Institute, Cleveland, Ohio. The study included adult subjects (i.e., 18 years or older) receiving OCT examination as standard-of-care management for retinal diseases.^{15,16} The study was approved by the Cleveland Clinic Institutional Review Board and adhered to all the tenets of the Declaration of Helsinki. All participants gave written informed consent for study enrollment.

Patients were imaged with the Avanti RTVue XR HD (Optovue, Fremont, CA) and with the Cirrus HD-OCT system (Zeiss, Oberkochen, Germany). The Avanti system was equipped with SSADA software with bulk motion correction technology, operated at a rate of 70,000 A-scans per second. Scan sizes obtained included 3×3 mm, 6×6 mm and/or 8×8 mm scans centered at the fovea. OCT angiograms were automatically segmented into the superficial retina, deep retina, outer retina, and choriocapillaris layers by the Avanti system.

This investigation was a subanalysis of the AVATAR study; subjects enrolled in the AVATAR study with indeterminate CNV were identified based on SD-OCT characteristics and underlying diagnosis. “Indeterminate CNV” was defined as eyes in which: 1) CNV was considered as part of the differential diagnosis based on SD-OCT and FA imaging, if obtained, 2) the presence of CNV was not clear based on imaging and/or clinical exam. Patients were excluded from the study if the clinical differential diagnosis included macular telangiectasia type 2.¹⁶ Additional exclusion criteria were insufficient quality of OCTA and/or previous anti-vascular endothelial growth factor (VEGF) therapy. For patients with bilateral eligible eyes, only 1 eye with worse SD-OCT clinical appearance (based on the

amount of material and/or fluid accumulation and RPE integrity) was included in the analysis.

OCTA and SD-OCT image review

All images were reviewed by two independent masked expert graders (AU, DM). A third independent grader (JPE) was employed to make an agreement when the agreement was unmet between the two graders. Segmented OCTA scans were assessed for the presence or absence of CNV, defined as flow signal in the outer retina and/or aberrant flow signal in the choriocapillaris consistent with known morphologies of CNV (Figure 1). The identification of CNV on OCTA was primarily determined by morphological characteristics of CNV as described in previous reports.^{11–13,17–24} The existence of type 1 CNV was considered highly probable when previously described morphological characteristics such as “lacy-wheel,” “sea-fan shaped” or “dead-tree appearance” was observed on en face OCTA scan and when abnormal flow was observed between RPE and Bruch’s membrane on corresponding cross-sectional OCTA.^{17–19} For type 3 neovascularization, the existence of pathologic flow signal in the outer retina was carefully explored and analyzed, meticulous attention was paid not to confound neovascularization with reflection from migrated RPE cells or projection artifact from inner retinal vessels.^{20–22,25,26} Additionally, distinct known artifacts of OCTA such as projection artifacts (decorrelation tails), motion artifacts were carefully identified.²⁷ For eyes in which the automatically segmented OCTA scans were indeterminate for the presence or absence of CNV, volumetric review with manual boundary segmentation was performed to confirm the absence of CNV. As for SD-OCT review, the macular cube, thickness map, five-line horizontal raster and five-line vertical raster scans were assessed for the presence or absence of intraretinal fluid, subretinal fluid, subretinal hyperreflective material (e.g., reticular pseudodrusen and vitelliform lesion), sub-RPE material (including large/confluent drusen), serous PED, shallow irregular PED, vitreomacular adhesion (VMA), epiretinal membranes (ERM) and/or RPE atrophy. Central subfield retinal thickness (the mean thickness in the 1 mm foveal area) was also measured. Eyes that showed heterogeneous reflective patterns within the PED, suggestive of vascularized PED were not included.

Statistical analysis

Data analyses were performed using R software version 3.2.3 (Software Foundation’s GNU project, <https://www.r-project.org/>).²⁸ The demographic characteristics and features on SD-OCT of the two patient group (presence or absence of CNV on OCTA) were compared using Mann-Whitney U test for continuous variables and Fisher’s exact test for categorical variables. SD-OCT features examined in the analysis included presence of intraretinal fluid, subretinal fluid, subretinal material, sub-RPE material, serous PED, VMA, ERM, RPE atrophy and select combinations of these features, as given in Table 1. Univariate logistic regression analysis was performed to evaluate the predictive value of single or combined structural features on SD-OCT for the presence of CNV on OCTA. All results were reported as odds ratio (OR) with 95% confidence interval (CI). In the multivariate analysis, adjusted OR and 95% CI for the presence of CNV on OCTA were estimated with logistic regression models to examine the effect of potential confounding factors (age, gender and central subfield retinal thickness) on the unadjusted results. The statistical significance was defined as $p < 0.05$.

Results

Among 247 patients participated in the AVATAR study between June 2015 and December 2016, twenty-nine eyes of 29 patients (13 male and 16 female patients) met the criteria for indeterminate CNV without previous history of anti-VEGF treatment. Seventeen (59%) eyes were evaluated with FA, while 12 (41%) eyes were evaluated with SD-OCT only.

Differential diagnosis included non-neovascular AMD (15 eyes), possible neovascular AMD (24 eyes), chronic CSCR (7 eyes), diabetic macular edema (1 eye), adult-onset foveomacular vitelliform dystrophy (5 eyes). The patient demographics and SD-OCT characteristics included in this study are given in Table 1 (patients were divided into two groups, depending on the presence of CNV on OCTA). The mean age of subjects was 77 ± 10 years (range 55 to 93 years). The mean central subfield retinal thickness was $279 \pm 62 \mu\text{m}$ (range 170 to 468 μm). The intraretinal fluid was present on SD-OCT in 8 (28%) eyes, and subretinal fluid was present in 16 (55%) eyes, of which 2 (7%) eyes had both intraretinal and subretinal fluid. The subretinal material was present in 20 (69%) eyes, and sub-RPE material was present in 23 (79%) eyes; 17 (59%) eyes presented with material in both locations. Serous PED, shallow irregular PED, VMA, ERM and RPE atrophy were present in 3 (10%), 8 (28%), 4 (14%), 4 (14%) and 8 (28%) eyes, respectively. Shallow irregular PED was the only single independent variable to demonstrate statistical significance between two groups ($p = 0.001$). In addition, combined presentations of intraretinal fluid and sub-RPE material was significantly associated with CNV on OCTA ($p=0.034$).

Eight (28%) of 29 eyes with clinically indeterminate CNV were positive for CNV on OCTA, which presented as an abnormal flow signal located in the outer retina (2 eyes), between the RPE and Bruch's membrane (4 eyes), and the choriocapillaris (2 eyes). The underlying differential diagnosis was AMD (neovascular/non-neovascular, 8 eyes), CSCR (2 eyes), adult onset foveomacular dystrophy (1 eye), and diabetic macular edema (1 eye). As for the morphological appearance of CNV, the margin was well circumscribed in 5 eyes and poorly circumscribed in 3 eyes. Figure 2 shows representative 2 cases with positive CNV on OCTA with a history of non-neovascular AMD. Although CNV existence was indeterminate on both early/late FA and spectral-domain OCT, OCTA scans of the outer retina and/or choriocapillaris revealed CNV membrane.

The remaining 21 (72%) eyes were negative for CNV on OCTA. Figure 3 illustrate 2 cases with unidentifiable CNV on OCTA with a history of non-neovascular AMD. CNV existence was inconclusive on early/late FA and spectral-domain OCT. CNV was not identified on OCTA scans of the outer retina and/or choriocapillaris.

Anti-VEGF treatment was performed in 3 (10%) eyes on the same day of study visit. In one eye with identifiable CNV on OCTA (Figure 4, 4E-G), the significant efficacy of anti-VEGF treatment with flattening of the PED and improvement of intraretinal edema further helped to confirm the presence of type 3 neovascularization. In another eye with CNV on OCTA (Figure 2E-G), anti-VEGF treatment was effective to decrease macular edema which supported the presence of CNV. One eye without CNV on OCTA underwent anti-VEGF treatment due to staining of fibrovascular PED on FA, however, the anatomical improvement was minimal. The 6 eyes with identifiable CNV on OCTA but did not initiate anti-VEGF

treatment were carefully monitored for the progression of the disease, and 3 eyes (Figure 5, 5B-C and 5G) later initiated anti-VEGF treatment (with an interval of 20, 4 and 15 months of observation, respectively). To date, 3 eyes have been monitored without treatment (Figure 5A, 5F and 5H), although one eye developed exudative changes after 17 months of follow-up (Figure 2D).

Results of the univariate and multivariate logistic regression analyses are given in Table 2. Among SD-OCT characteristics, the presence of a shallow irregular PED was significantly predictive of the presence of CNV on OCTA [OR, 28.5; 95% CI, 3.27–248; $p = 0.002$]. Additionally, SD-OCT combined presentations of intraretinal fluid and sub-RPE material were also significantly correlated with positive CNV on OCTA [OR, 9.50; 95% CI, 1.27–71.0; $p = 0.028$]. These associations were maintained in multiple logistic regression [shallow irregular PED; OR, 148; 95% CI, 3.22–6830; $p = 0.011$] [Intraretinal fluid + Sub-RPE material; OR, 16.8; 95% CI, 1.43–198; $p = 0.025$], after adjusted for age, gender, and central subfield retinal thickness.

Discussion

In this study, we used OCTA to evaluate eyes with indeterminate CNV features on clinical exam and prior diagnostic imaging. In this setting, OCTA was successfully detected CNV in 28% of eyes. Utilizing OCTA as an additional modality may be an important addition to the diagnostic and treatment surveillance approach of CNV-related diseases, such as neovascular AMD. Besides shallow irregular PED, the combined presence of intraretinal fluid and sub-RPE material on SD-OCT may be regarded as an important predictor of CNV on OCTA in eyes with indeterminate CNV.

The strengths of the current investigation are that this was a subanalysis of the prospective study. To the best of our knowledge, OCTA on indeterminate CNV in treatment naïve patients has not been explored in prior reports. Our OCTA and SD-OCT instruments are latest generation system that are commercially available. For OCTA image analysis, the manual technique was carefully employed for retinal layer segmentation in required patients to achieve the best chance of CNV detection.

The detection rate of CNV on OCTA appears to vary among different retinal disorders and perhaps OCTA platforms. Recently, de Carlo et al studied 30 eyes with or without CNV on a prototype OCTA system and performed same-day FA to evaluate sensitivity and specificity of CNV detection on OCTA.¹² The authors reported a relatively low sensitivity of 50% and high specificity of 91% and suggested that OCTA could be beneficial for detecting CNV with undetermined diagnosis by other methods. In their report, 75% of false-negative cases had a large amount of subretinal hemorrhage, which blocked OCT signals. In another study, Coscas et al investigated 80 eyes of exudative AMD using an OCTA prototype instrument and indicated that lacy-wheel or sea-fan shaped typical neovascular lesion was confirmed in 59 (74%) eyes.¹⁷ Meanwhile, Bonini Filho et al conducted OCTA prototype on 27 eyes with PED secondary to chronic CSCR.¹³ With concurrent standard assessment (including FA) for possible CNV, the authors reported that sensitivity and specificity of CNV detection on OCTA were both 100%.¹³ The discrepancy in sensitivity between these studies implies that

CNV becomes less detectable on OCTA when RPE plane is highly distorted and/or elevated due to sub-RPE deposits/fluids, or when OCT signals are blocked by retinal hemorrhages. Also, the location of CNV search and exact segmentation of retinal layers would be critically important to identify CNV on OCTA.^{11–13,27} Most OCTA software review platforms allow for manual correction of the segmentation line to maximize the area of sampling and region of interest. This may also play a role in detection rate. The present study differs from others in that it investigates only indeterminate CNV with conventional diagnostic tools, more precisely, eyes with subretinal hemorrhage on the fundus image or vascularized PED appearance on SD-OCT suggestive of the neovascular membrane were not included in this analysis. Our study population consisted of multiple differential diagnoses may be closer to real-life clinical monitoring settings compared with previous reports, so that our CNV detection rate of 28% on OCTA is noteworthy.

Among 8 eyes with positive CNV on OCTA, 2 eyes had type 3 neovascularization in the outer retinal layers. In one eye (Figure 4A-D), the large hyperreflective focus was observed at the apex of drusenoid PED with downward deflection of the outer plexiform layer,²⁹ indicative of precursor lesion on cross-sectional OCT. The existence of neovascularization was indeterminate with conventional diagnostic exams, however, hyper-flow signal corresponding to the lesion led to the diagnosis. Nevertheless, the possibility of projection artifact cannot be excluded given the fact that the eye did not exhibit exacerbation of exudative changes throughout the observational period of 22 months. In another eye (Figure 4E-G), abnormal flow was observed in the retinal deep capillary plexus involving significant macular edema and disruption of the RPE. The remaining 6 cases were all type 1 CNV, localized between the RPE and Bruch's membrane in 4 eyes and the choriocapillaris in 2 eyes. In one eye (Figure 2A-D), the presence of geographic atrophy made the diagnosis of CNV with OCTA particularly challenging. Nesper et al recently demonstrated that when larger choroidal vessels are anteriorly displaced replacing choriocapillaris in the areas of geographic atrophy, it may become difficult to distinguish CNV from the residual choroidal vasculature.²⁴ In this case, since there was little amount of abnormal flow above Bruch's membrane, it is possible that not all components of CNV were above Bruch's membrane, and some of the abnormal vasculatures on en face OCTA may represent CNV that has not infiltrated above the Bruch's membrane.²⁴ The eye developed exudative changes after 17 months of observation with visual acuity of 20/200. Anti-VEGF treatment was not performed due to patient's preference. No type 2 CNV were identified in this study, presumably because type 2 CNV may have been easier to diagnose as "determinate CNV" due to its distinct appearance on FA and concurrent intraretinal hemorrhage.

The reason why we could not find any CNV in 72% of our 29 cases can be attributed to either a limitation of the current technology for OCTA or a true absence of CNV. OCTA imaging is a nascent, developing technology, it is possible that CNV was not detected due to segmentation error, obscured by projection/motion artifacts, or low blood flow speed within the CNV.^{12,13,27} As no CNV virtually exist in the coplanar plane, meticulous attention was paid to the segmentation process, however, segmentation along the slope of PED elevation was difficult because the shape of automatically detected sliced lines delineating the region of interest could not be corrected manually. Dynamic adjustment of the segmentation boundaries are warranted for accurate detection of CNV and interpretation of the results.

In this report, shallow irregular PED on SD-OCT was associated with the presence of CNV on OCTA. In fact, shallow irregular PED was present in all 6 eyes with type 1 CNV. Dansingani et al have previously studied 16 eyes with pachychoroid spectrum disease, and demonstrated that latent type 1 CNV was identified on OCTA in 95% of cases with shallow irregular PED.²³ Because the vascular network within shallow irregular PED are often underestimated on dye-based angiography,²³ shallow irregular PED would be particular region of interest on OCTA, if present. Interestingly, the select combination of SD-OCT characteristics, intraretinal fluid and sub-RPE material, was also correlated with the presence of CNV on OCTA in patients with clinically indeterminate CNV. This finding is particularly relevant in the context of decisions to treat suspected CNV lesions, which are commonly based on the presence of fluid on OCT as a marker of active exudation.⁸ The combined presence of intraretinal fluid and sub- RPE material are also consistent with the appearance of active type 1 (sub-RPE), type 2 (subretinal) neovascular lesions, and particularly type 3 neovascularization.³⁰ These features may help to raise the level of suspicion of underlying CNV in eyes without definitive CNV on exam or FA.

Limitations of this study include cross-sectional nature of the study and small sample size. Selection bias is another potential limitation of our study since FA was not performed to evaluate indeterminate CNV in all cases. Limitations of current OCTA technology include frequent image artifacts from vessel projection from the superficial retina onto the outer retina and choriocapillaris and the relatively small fields of view that can be imaged, which may lead to some peripheral CNV membranes being missed.³¹ Additionally, it is currently unknown whether CNV visualized on OCTA in the absence of exudative activity on SD-OCT or other conventional imaging should undergo treatment or observation.³² Further research is required to clarify the role of OCTA in CNV management.

OCTA appears to be a valuable tool in clarifying the diagnosis of CNV in patients with indeterminate prior imaging. The presentation of shallow irregular PED, or the combination of intraretinal fluid and sub-RPE material on SD-OCT may be suggestive of the presence of CNV in such patients. Further studies are required to delineate the specific role of OCTA in the management of patients with clinically indeterminate CNV.

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Abbreviations and Acronyms:

AMD	age-related macular degeneration
AVATAR	A prospective observational study examining OCTA in eyes undergoing routine SD-OCT for the macular disease
CI	confidence interval
CSCR	central serous chorioretinopathy

CNV	choroidal neovascularization
ERM	epiretinal membranes
FA	fluorescein angiography
OCT	optical coherence tomography
OCTA	optical coherence tomography angiography
OR	odds ratio
PED	pigment epithelial detachment
RPE	retinal pigment epithelium
SD-OCT	spectral-domain optical coherence tomography
SSADA	split-spectrum amplitude- decorrelation
VEGF	vascular endothelial growth factor
VMA	vitreomacular adhesion

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Figure 1. Optical coherence tomography angiography (OCTA) of choroidal neovascularization (CNV).

A-B, Normal 3 × 3 mm OCTA *en face* scans and corresponding B scan with flow overlay segmented at the outer retina (**A**) and choriocapillaris (**B**) show no visible CNV. **C-D**, OCTA *en face* scans of the outer retina (**C**) and choriocapillaris (**D**) illustrate a large, well-circumscribed CNV membrane (arrow).

Figure 2. Choroidal neovascularization (CNV) visualized with optical coherence tomography angiography (OCTA) in eyes with previous indeterminate CNV.

A-D, The right eye of a 93-year-old female, with a history of non-neovascular age-related macular degeneration (AMD). Early and late fluorescein angiography (FA) revealed pigment blocking an area of indeterminate leakage (arrowhead) (**A**). The vertical SD-OCT scan showed subfoveal atrophic changes, intraretinal fluid-filled cysts (arrowheads), and hyperreflective material below the RPE (arrow) without obvious neovascularization (**B**). The intraretinal cysts may be attributed to both degenerative and exudative changes. OCTA segmented at the outer retina and the choriocapillaris revealed a noticeable CNV (outline) with a surrounding halo of vessel dropout in the choriocapillaris. Given the little amount of abnormal flow above Bruch's membrane, it is possible that some of the abnormal vasculatures may represent CNV that has not infiltrated above the Bruch's membrane. Also, the possibility of anterior displacement of larger choroidal vessels replacing choriocapillaris in the area of geographic atrophy, or remodeling of the remaining choroidal vessels cannot be excluded. Projection artifacts from the superficial retinal layers were also visible (asterisks) (**C**). The eye exhibited exudative changes as shown in the vertical SD-OCT scan after 17 months of observation with visual acuity of 20/200. Anti-VEGF treatment was not performed due to patient's preference (**D**). **E-G**, The left eye of a 92-year-old female with advanced non-neovascular AMD. Early and late FA demonstrated extensive hyperfluorescence without obvious neovascularization (**E**). The vertical SD-OCT scan revealed extrafoveal geographic atrophy, intraretinal fluid-filled cysts, (arrowheads) and sub-RPE deposits (arrows) (**F**). OCTA segmented at the outer retina and choriocapillaris revealed a filamentous CNV lesion (arrowheads) (**G**).

Figure 3. Optical coherence tomography angiography (OCTA) without choroidal neovascularization (CNV) in eyes with previous indeterminate CNV.

A-C, In a patient with a history of non-neovascular age-related macular degeneration (AMD) in both eyes and subretinal fluid on previous SD-OCT imaging, early and late fluorescein angiography (FA) images showed a large central area of hyperfluorescence (arrowhead) with staining but no obvious leakage (**A**). SD-OCT vertical raster scan revealed subretinal fluid (white arrows) and subretinal and sub-RPE material (black arrows) (**B**). OCTA demonstrated an area of choriocapillaris alteration centrally but no obvious CNV (**C**). **D-F**, In another patient with a history of vitelliform-like lesions on prior SD-OCT imaging, FA demonstrated late areas of hyperfluorescence (arrowheads) indicating possible occult leakage versus staining (**D**). The vertical SD-OCT scan revealed a serous pigment epithelial detachment with associated subretinal fluid (arrow) (**E**), however, no CNV lesions were found on OCTA segmented at the outer retina and choriocapillaris (**F**).

Figure 4. Two eyes of type 3 neovascularization identified with optical coherence tomography angiography (OCT).

A-D, The right eye of an 84-year-old male. Clinical differential diagnosis included non-neovascular age-related macular degeneration (AMD), asymptomatic neovascular AMD and non-proliferative diabetic retinopathy. No active leakage is observed in the early phase fluorescein angiography. The circle corresponds to the location of abnormal flow on OCTA (**A**). Multiple drusenoid pigment epithelial detachment (PED) and cystic macular edema are seen on horizontal SD-OCT (**B**). Abnormal flow can be observed in *en face* OCTA of the deep inner retina slab (circle), as well as close to the top of drusenoid PED (arrowhead) in cross-sectional OCTA (**C**). Downward deflection of the outer plexiform layer (arrow) is present, suggestive of a precursor lesion of type 3 neovascularization. The projection artifact from the inner retinal vessels are excluded since no major retinal vessels cross the site in the superficial inner retina slab (circle) (**D**). However, the possibility of artifact due to the reflection of migrated retinal pigment epithelial cells, or abnormal vascular formation associated with diabetic retinopathy cannot be fully excluded. **E-G**, The left eye of a 72-year-old male with an indeterminate clinical diagnosis of neovascular AMD. Fluorescein angiography was not performed for this patient. Abnormal flow is observed in the retinal deep capillary plexus (arrow and arrowhead) involving significant macular edema and disruption of the retinal pigment epithelium (**E**). This patient received anti-vascular endothelial growth factor (VEGF) treatment on the same day of study visit. After 6 months of 3 anti-VEGF injections, the significant anatomical improvement with flattening of the PED and resolution of macular edema was observed, which further helped to confirm the

presence of type 3 neovascularization. The retinal thickness map obtained with SD- OCT; before (**F**), and 6 months after the treatment (**G**).

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Figure 5. Optical coherence tomography angiography (OCTA) of 8 eyes with identifiable choroidal neovascularization (CNV).

A-H, En face OCTA of the inner retina and choriocapillaris scans and corresponding crosssectional OCT with decorrelation overlay are shown for all 8 eyes with identifiable CNV. **A**. Right eye of an 84-year-old male. **B**. Right eye of an 82-year-old female. **C**. Right eye of a 63-year-old female. **D**. Left eye of a 92-year-old female. **E**. Left eye of a 72-year-old male. **F**. Right eye of a 93-year-old female. **G**. Left eye of a 62-year-old male. **H**. Left eye of a 55-year-old female.

Table 1:

Demographics and OCT characteristics in patients with clinically indeterminate CNV

Variables	Presence of CNV on OCTA		<i>p</i> value
	CNV (+) (8 eyes)	CNV (–) (21 eyes)	
Age (years)	75 ± 14	77 ± 8	0.961
Gender, number of female eyes (%)	5 (63)	11 (52)	NS
Central subfield retinal thickness (pm)	301 ± 78	271 ± 54	0.464
SD-OCT characteristics, number of eyes (%)			
Intraretinal fluid	4 (50)	4 (19)	0.164
Subretinal fluid	4 (50)	12 (57)	NS
Subretinal material	5 (63)	15 (71)	0.675
Sub-RPE material	8 (100)	15 (71)	0.148
Serous PED	1 (13)	2 (10)	NS
Shallow irregular PED	6 (75%)	2 (10)	0.001
VMA	2 (25)	2 (10)	0.300
ERM	1 (13)	3 (14)	NS
RPE atrophy	2 (25)	6 (29)	NS
Intraretinal fluid + Subretinal material	2 (25)	2 (10)	0.300
Intraretinal fluid + Sub-RPE material	4 (50)	2 (10)	0.034
Subretinal fluid + Subretinal material	3 (38)	9 (43)	NS
Subretinal fluid + Sub-RPE material	4 (50)	9 (43)	NS
Intraretinal fluid + Subretinal fluid + Subretinal material + Sub-RPE material	1 (13)	1 (5)	0.483

CNV = choroidal neovascularization; ERM = epiretinal membrane; NS = not significant; OCTA = optical coherence tomography angiography; PED = pigment epithelial detachment; RPE = retinal pigment epithelium; SD-OCT = spectral-domain optical coherence tomography; VMA = vitreomacular adhesion. Results of continuous variables are expressed as mean ± standard deviation.

Table 2:

Univariate and multivariate logistic regression analysis for the presence of CNV on OCTA in patients with clinically indeterminate CNV

Variables	Univariate		Multivariate, adjusted	
	Odds ratio [95% CI]	<i>p</i> value	Odds ratio [95% CI]	<i>p</i> value
Age	0.982 [0.905 – 1.07]	0.660	–	–
Gender, female	1.52 [0.286 – 8.03]	0.625	–	–
Central subfield retinal thickness	1.01 [0.994 – 1.02]	0.258	–	–
SD-OCT characteristics				
Intraretinal fluid	4.25 [0.729 – 24.8]	0.108	5.11 [0.728 – 35.8]	0.101
Subretinal fluid	0.750 [0.146 – 3.84]	0.730	0.744 [0.134 – 4.13]	0.735
Subretinal material	0.667 [0.120 – 3.71]	0.643	0.561 [0.0803 – 3.92]	0.560
Sub-RPE material	6.17×10^7 [0 – infinity]	0.995	5.86×10^7 [0 – infinity]	0.995
Serous PED	1.36 [0.106 – 17.4]	0.815	1.52 [0.111 – 20.7]	0.754
Shallow irregular PED	28.5 [3.27 – 248]	0.002	148 [3.22 – 6830]	0.011
VMA	3.17 [0.364 – 27.6]	0.297	6.66 [0.362 – 123]	0.202
ERM	0.857 [0.0758 – 9.70]	0.901	0.693 [0.0498 – 9.65]	0.785
RPE atrophy	0.833 [0.130 – 5.35]	0.848	1.22 [0.159 – 9.40]	0.846
Intraretinal fluid + Subretinal material	3.17 [0.364 – 27.6]	0.297	3.02 [0.317 – 28.8]	0.336
Intraretinal fluid + Sub-RPE material	9.50 [1.27 – 71.0]	0.028	16.8 [1.43 – 198]	0.025
Subretinal fluid + Subretinal material	0.800 [0.150 – 4.26]	0.794	0.640 [0.104 – 3.94]	0.631
Subretinal fluid + Sub-RPE material	1.33 [0.260 – 6.83]	0.730	1.31 [0.226 – 7.53]	0.765
Intraretinal fluid + Subretinal fluid + Subretinal material + Sub-RPE material	2.86 [0.157 – 52.1]	0.478	2.78 [0.150 – 51.5]	0.493

CI = confidence interval; CNV = choroidal neovascularization; OCTA = optical coherence tomography angiography; PED = pigment epithelial detachment; RPE = retinal pigment epithelium; SD-OCT = spectral-domain optical coherence tomography; VMA = vitreomacular adhesion.