DETECTION OF NONEXUDATIVE CHOROIDAL NEOVASCULARIZATION IN AGE-RELATED MACULAR DEGENERATION WITH OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

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Purpose: To evaluate eyes with age-related macular degeneration and high-risk characteristics for choroidal neovascularization (CNV) with optical coherence tomographic (OCT) angiography to determine whether earlier detection of CNV is possible.

Methods: Eyes with drusen, pigmentary changes, and with CNV in the fellow eye were scanned with a 70-kHz spectral domain OCT system (Optovue RTVue-XR Avanti). The split-spectrum amplitude-decorrelation angiography (SSADA) algorithm was used to distinguish blood flow from static tissue. Two masked graders reviewed scans for CNV, defined as flow in the outer retinal/sub-RPE slab. Choroidal neovascularization flow area repeatability and between-grader reproducibility were calculated.

Results: Of 32 eyes, 2 (6%) were found to have Type 1 CNV with OCT angiography. The lesions were not associated with leakage on fluorescein angiography or fluid on OCT. One case was followed for 8 months without treatment, and the CNV flow area enlarged slightly without fluid buildup on OCT or vision loss. Between-grader reproducibility of the CNV flow area was 9.4% (coefficient of variation) and within-visit repeatability was 5.2% (pooled coefficient of variation).

Conclusion: Optical coherence tomographic angiography can detect the presence of nonexudative CNV, lesions difficult to identify with fluorescein angiography and OCT. Further study is needed to understand the significance and natural history of these lesions.

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Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in the United States in individuals aged 65 years and older. Neovascular AMD accounts for approximately 15% of AMD cases and makes up most cases with vision loss.[1] Choroidal neovascularization (CNV) in the fellow eye is an established risk factor for the development of neovascularization with an annual incidence ranging between 4% to 19%.[2–4] With advancements in diagnostic imaging, screening this population for early detection of CNV is becoming increasingly important as it may have both therapeutic and prognostic implications.

Structural optical coherence tomography (OCT) is used routinely to detect and monitor exudative changes in neovascular AMD.[5] En face spectral domain (SD) OCT has demonstrated vascular structure within pigment epithelial detachment (PED).[6] However, the ability to discriminate pathologic CNV from choroidal vasculature, fibrotic PEDs, and fibrinous

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material is limited.[7] Invasive dye-based angiography with either fluorescein angiography (FA) or indocyanine green angiography remains the gold standard to diagnose CNV.[8]

Recently, OCT angiography methods have been developed providing noninvasive 3D angiograms of retinal and choroidal blood vessels. We recently developed the split-spectrum amplitude-decorrelation angiography (SSADA) algorithm that detects motion within the blood vessel lumen by measuring the variation in reflected OCT signal amplitude between consecutive cross-sectional B-scans. Improved image quality is achieved by splitting the OCT signal into multiple spectral bands, increasing the signal-to-noise ratio.[9–11] The SSADA algorithm enabled high-quality and relatively wide-field OCT angiography using speeds available on a commercial retinal OCT system.[12]

Detection of CNV in neovascular AMD with SSADA has been demonstrated with both a high-speed prototype swept-source OCT and a commercially available SD-OCT.[13,14] Optical coherence tomographic angiography is noninvasive and allows for rapid image acquisition, making it potentially useful to screen eyes at risk for CNV. We recently designed and implemented a longitudinal study using OCT angiography to screen eyes with high risk for developing advanced AMD based on having exudative AMD in the fellow eye, as well as drusen and pigmentary changes, which were well recognized risk factors from AREDS.[1] In this article, we report findings from our baseline screening visit and describe two cases of clinically silent CNV detected with OCT angiography.

Methods

Study participants were recruited from the retina clinics at the Casey Eye Institute (Oregon Health and Science University, Portland, OR) from September 2014 to May 2015. They were enrolled in a longitudinal study of 3-year duration after informed consent was obtained in accordance with the Institutional Review Board of the Oregon Health and Science University. Optical coherence tomographic angiography is an off-label use of the RTVue-XR Avanti OCT system (Optovue, Inc, Fremont, CA). In this article, results from baseline screening are reported. Study participants were required to have exudative neovascular AMD in one eye and nonexudative AMD in the other eye documented by both drusen and retinal pigment epithelial (RPE) changes. Visual acuity, dilated fundus examination, structural SD-OCT (Spectralis, Heidelberg Engineering, Germany), and OCT angiography scans were obtained at baseline and at subsequent 6-month intervals. The exclusion criteria for the nonexudative AMD eye included visual acuity worse than 20/200 using the Early Treatment Diabetic Retinopathy Study chart, presence of subretinal hemorrhage or lipid exudate on clinical examination, and presence of subretinal fluid/intraretinal fluid (SRF/IRF) on SD-OCT. If CNV is detected by OCT angiography but is not detectable on dilated fundus examination and SD-OCT, then management and further ancillary testing including FA is at the discretion of the treating physician. Follow-up OCT angiography scans were obtained at subsequent routine follow-up visits to monitor the natural history of the nonexudative CNV lesion.

Optical coherence tomographic angiography was performed with the RTVue-XR Avanti (Optovue, Inc), which is a 70-kHz SD-OCT system with a spectrum centered at 840-nm wavelength and an axial resolution of 5 μm full-width-half-maximum in tissue. Two OCT angiography scans were collected at each visit. Each OCT angiography scan consists of one volumetric horizontal priority (x-fast) and one volumetric vertical priority (y-fast) raster scan. For each volumetric scan, there are 304 A-scans per B-scan, and 2 consecutive B-scans at 304 locations. For each OCT voxel, SSADA detects the speckle decorrelation value, which is related to the velocity of motion or flow. Subsequent processing of the SSADA angiogram can provide measurement of the vascular area with active flow within defined tissue slabs. Briefly, SSADA goes pixel by pixel and assesses the OCT reflectance variation between the two consecutive B-scans at each location through decorrelation to differentiate between flow (high decorrelation) and static tissue (low decorrelation). Split-spectrum processing is used to improve the signal-to-noise ratio of flow detection.[9–11] To correct for motion artifacts, the contained software registered and merged the x-fast and y-fast scans.[15]

En face view of the tissue structure was generated by mean reflectance intensity projection. En face OCT angiograms were generated by maximum decorrelation (flow) projection in the following slabs: 1) the inner retina from the internal limiting membrane to the outer plexiform layer (OPL); 2) the outer retina/sub-RPE form the outer boundary of OPL to the Bruch membrane (BM); and 3) the choriocapillaris 10 μm to 20 μm below BM.

Two experienced graders (S.S.G. and N.V.P.) examined the OCT angiograms while masked to the identity, diagnosis, and scan date. The 2 graders had cumulatively reviewed over 150 OCT angiograms before the study. En face images were presented to graders on PowerPoint (Microsoft, Seattle, WA) slides. Graders were provided an en face structure

OCT (C-scan) image of the RPE layer to identify any irregularities in the reflectance pattern, in addition to segmented en face OCT angiograms described above. The graders looked for abnormal vascular complexes within the outer retinal/sub-RPE slab. To mitigate the potential confounding effects of inner retinal vasculature projection artifacts onto the RPE, the graders also examine the en face angiogram of the outer retinal/sub-RPE slab with the inner retinal projection artifacts subtracted by automated image processing. Because CNV projects onto the choriocapillaris slabs underneath, the choriocapillaris slabs were included for the graders to review. For a case to be graded as a candidate CNV, a vascular network had to be present in both the outer retina/sub-RPE slab and may or may not be present in the choriocapillaris slab. Examples of images available to graders are shown in Figure 1. If graders did not agree, then an additional grader (Y.J.) served as a tiebreaker. For cases identified as having CNV detected with OCT angiography, two investigators (S.T.B. and N.V.P.) reviewed structural SD-OCT images to confirm the absence of IRF/SRF and reviewed FA to confirm the absence of leakage.

If a scan was graded as a candidate CNV, the grader then reviewed composite gray-scale cross-sectional structural images with color flow overlay to determine whether the CNV was below or above RPE and classify it as Type I or Type II CNV accordingly. In addition, the grader decided whether the CNV area could be calculated based on the signal strength index (SSI, calculated by the scanning software) of the scan and observed residual motion artifacts. If the scan was deemed good quality (SSI $>$ 50 and few residual artifacts), the grader would then contour the CNV in the choriocapillaris angiogram using custom software written in MATLAB (Mathwords, Natick, MA). The CNV area was calculated based on a binary image of the contoured area. Pixels within the CNV contour area with decorrelation (flow) values above a threshold of 0.069 were summed to provide the CNV area. The CNV area represents the total area of vessels with active blood flow within the CNV network. The threshold was set such that it minimized the smaller vessel projection artifacts while maintaining the vascular shape of the observed CNV. To create composite en face angiograms of the inner retina and CNV, the inner retina angiogram (purple) was overlaid on the contoured CNV (yellow).

At each visit, 2 OCT angiography scans were obtained and 2 graders with experience (20 cases and 10 cases, respectively) independently countered the CNV on both OCT angiography scans provided the quality criteria was satisfied. To assess for within-visit repeatability and between-grader reproducibility, the intraclass correlation (ICC) and coefficient of variation was calculated using SPSS 20 (IBM, Armonk, NY).

Results

Thirty-four consecutive study participants were enrolled, of which 53% were female and the mean age was 79 years (range 57–89, SD 8 years). Mean Early Treatment Diabetic Retinopathy Study visual acuity was 20/25 (79 letters).

Two participants were excluded from this analysis because of poor image quality in the study eye. In one case, posterior subcapsular cataract produced shadow artifact, and in the other, poor fixation due to center involving geographic atrophy resulted in excessive motion artifact.

Both graders reviewed images independently and were in agreement in all cases. Thirty of the 32 study eyes were found to have no CNV present at the baseline visit. Figure 1 provides representative OCT

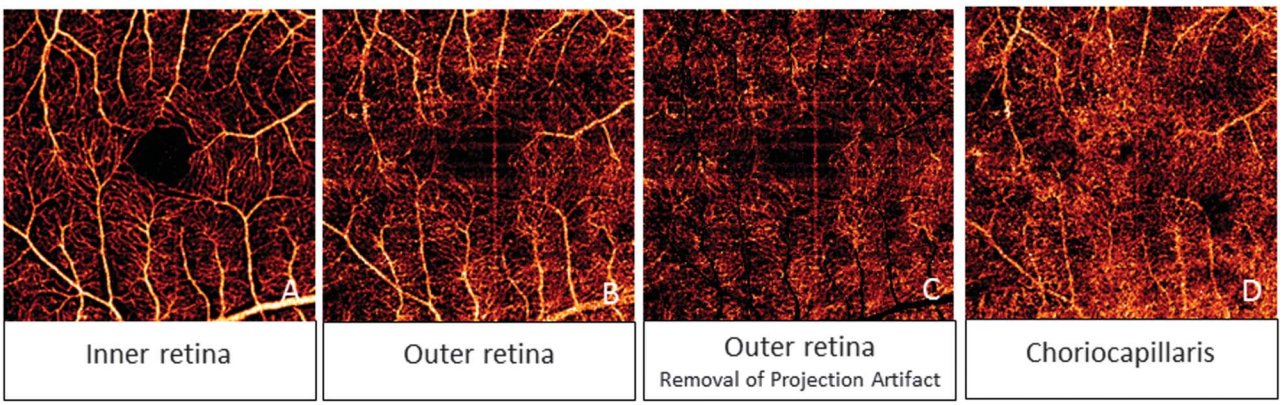

Fig. 1. Example of high-risk AMD without CNV. **A.** Inner retinal OCT angiogram (en face). **B.** Outer retinal/sub-RPE OCT angiogram. **C.** Outer retinal/sub-RPE OCT angiogram with suppression of inner retinal vessel projection artifact by an automated computer algorithm. **D.** Choriocapillaris OCT angiogram.

angiograms of an eye without CNV. Two eyes were identified to have a vascular network in the outer retinal/sub-RPE OCT angiogram consistent with a CNV. Further details of these two cases are reported below. At baseline, the rate of nonexudative CNV detected with OCT angiography in this series was 2 of 32 eyes, or 6.25%.

Twenty-eight participants were receiving intravitreal antivascular endothelial growth factor agents in their fellow eye for treatment of exudative neovascular AMD: 35% bevacizumab, 11% ranibizumab, and 35% aflibercept.

Choroidal Neovascularization Flow Area Repeatability and Between-Grader Reproducibility

Between-grader reproducibility was assessed by pooling CNV area measurements from 15 scans from the 2 cases of nonexudative CNV. The coefficient of variation was 9.4%, and the ICC was 0.92. Within-visit repeatability was assessed in the 5 visits with 2 gradable scans. The coefficient of variation was 3.3% and 6.6% for the 2 graders, and the pooled coefficient of variation was 5.2%. The ICC was 0.99 and 0.91 for the 2 graders, and the pooled ICC was 0.96. Two scans were not graded because of low SSI, and three scans were not graded because of severe residual motion artifacts.

Case Descriptions

Case 1. An 88-year-old white woman presented with reduced vision in her right eye secondary to exudative neovascular AMD. The Early Treatment Diabetic Retinopathy Study visual acuity measured 20/125 and 20/25 in the right and left eye, respectively. Fundus examination revealed bilateral drusen and pigmentary changes with perifoveal geographic atrophy in the left macula (Figure 2A). In the left eye, FA performed 1 month before OCT angiography did not show any evidence of fluorescein leakage (Figure 2, B and C). Optical coherence tomographic angiography revealed a small vascular network in the outer retinal/sub-RPE slab nasal to the area of geographic atrophy (Figure 2F). Choroidal neovascularization projection artifact was visible on the choriocapillaris slab as well (Figure 2G). Color-coded cross-sectional OCT angiograms combined with structural OCT localized the vascular network within PED between RPE and BM, consistent with a Type 1 CNV (Figure 2H). Color composite en face OCT angiogram localizes CNV to the nasal macula (Figure 2I). The patient has yet to return for follow-up to obtain serial images.

Case 2. A white male in his late 60s presented with vision loss in the right eye secondary to exudative neovascular AMD. Early Treatment Diabetic Retinopathy Study visual acuity measured 20/50 and 20/32 in his right and left eye, respectively. Fundus examination revealed bilateral drusen and pigmentary changes in the macula in both eyes (Figure 3A).

The left eye did not show any CNV on FA (no leakage) and lacked SRF/IRF on OCT (Figure 3, B and C, H). However, en face OCT angiograms revealed a vascular network in the outer retinal/sub-RPE slab (Figure 3F). Projection of the same CNV pattern was confirmed in the choriocapillaris angiogram (Figure 3G). Cross-sectional OCT angiogram localized the vascular network between RPE and BM consistent with Type 1 CNV (Figure 3H). Color composite en face OCT angiograms showed that the CNV was just inferior to the fovea (Figure 3I).

The left eye did not receive treatment and was monitored over 8 months with serial OCT angiograms. The average CNV flow area was 0.2 ± 0.02 mm^2 at baseline and increased to 0.24 ± 0.01 mm^2 at last follow-up (Figure 4, A–D). This 20% increase in the CNV flow area was significantly greater than the intravisit repeatability of 5.2%, which suggests that the observed growth is real. Throughout follow-up, there was no evidence of exudation on structural OCT (confirmed by S.T.B. and N.V.P.). Repeat FA 5 months after baseline visit revealed no evidence of late leakage. Final visual acuity was 20/25.

The right eye was treated with intravitreal bevacizumab using a treat-and-extend strategy. The follow-up visit interval increased with each visit, starting with 6 weeks after baseline visit with subsequent visit intervals extending to 7, 9, and 10 weeks, respectively. Structural OCT revealed resolution of SRF after the first treatment. The fluid returned at the last visit after the longest interval of 10 weeks. Serial OCT angiograms revealed fading of smaller peripheral CNV branches over time and a reduction in averaged CNV flow area from 0.39 ± 0.05 mm^2 at baseline to a nadir of 0.34 ± 0.03 mm^2 at the third study visit (after a treatment interval of 7 weeks). This 12.8% reduction in the CNV area was significant compared with the repeatability of 5.2%. However, the CNV area increased to 0.37 ± 0.02 mm^2 at last follow-up, after a treatment interval of 10 weeks (Figure 4, E–I). Visual acuity continually improved over the course of treatment and was 20/32 at the last visit.

Discussion

Fluorescein angiography detects CNV by identifying the presence of leakage from incompetent vascular

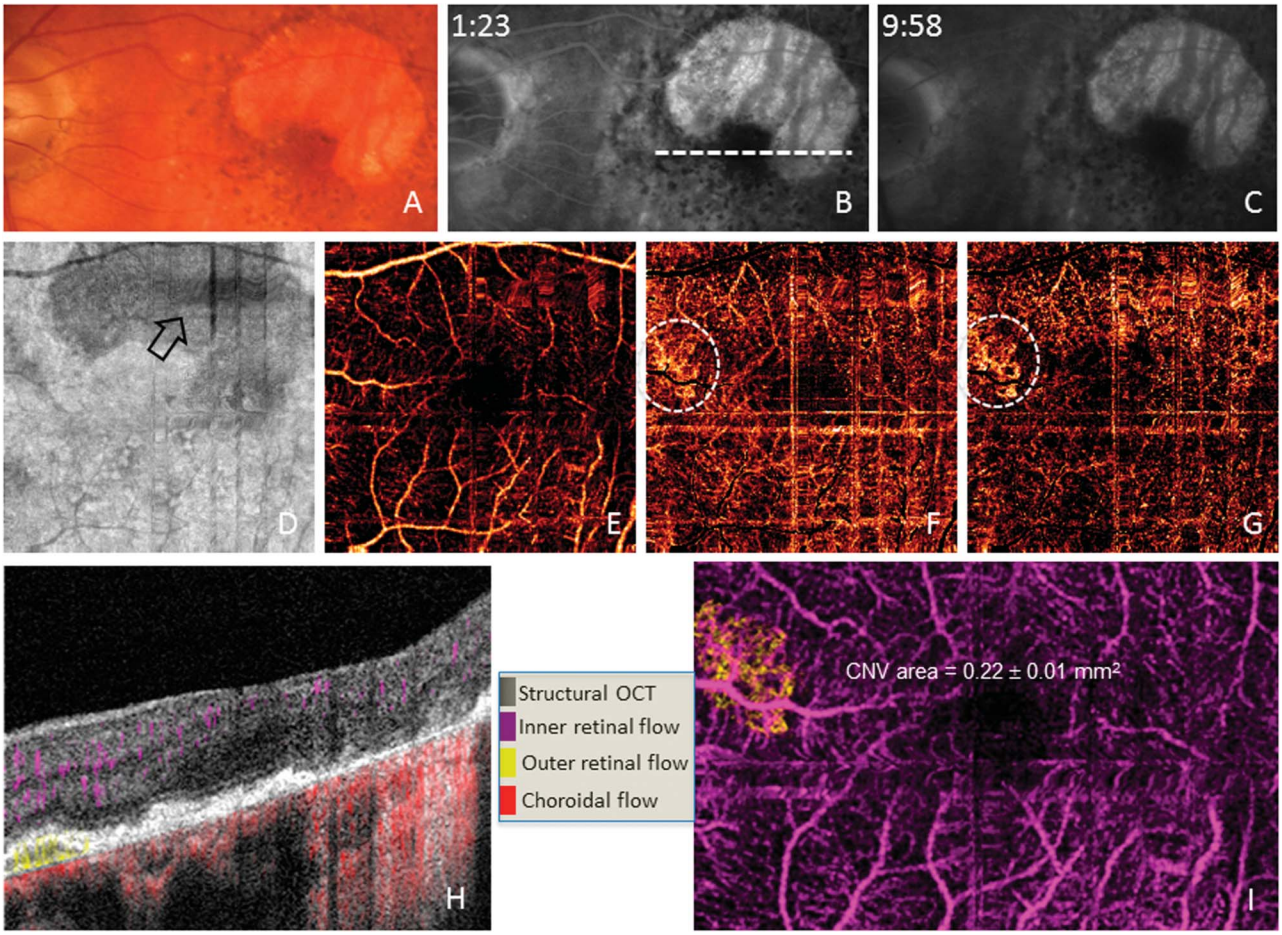

Fig. 2. Case 1 of nonexdudative CNV (left eye). **A.** Color photograph. **B** and **C.** Early- and late-phase fluorescein angiograms showing scattered staining of drusen and window defect in the area of RPE atrophy but no dye leakage. **D.** En face structural OCT of the RPE slab highlighting the area of geographic atrophy (arrow). **E.** Inner retinal OCT angiogram. **F.** Outer retinal OCT angiogram with CNV (white circle). **G.** Outer retinal/sub-RPE OCT angiogram with suppressed projection artifact. **G.** Choriocapillaris OCT angiogram with CNV (white circle). **H.** Color-coded cross-sectional OCT angiogram (position indicated by a white line on **B**) demonstrating type I CNV (yellow). **I.** Color composite en face OCT angiogram of retinal vessels (purple) and CNV (yellow). The numbers showed the mean ± SD of the CNV area.

tissue, and therefore, by definition, CNV seen on FA must be an "exudative" lesion. Optical coherence tomographic angiography detects CNV by the presence of abnormal pattern of vascular flow above the BM, and therefore it is possible to detect CNV that do not leak on FA. To our knowledge, this has not been demonstrated before.

We identified two cases of "nonexudative" CNV with OCT angiography. Both cases were Type 1 CNV, and neither had evidence of leakage on FA nor SRF/IRF on structural OCT. Histopathologic studies showed CNV to be a growing network of vessels under the RPE or retina emerging through breaks in the BM.[16] Neovascular endothelial cells lack the barrier function of more developed endothelial cells and can leak fluid, lipid, proteins, and blood cells. Fluorescein angiography used this characteristic of CNV to help identify neovascular tissue. Dye leaking from these vessels accumulates in the sub-RPE or subretinal space and can be visualized during angiography. Similarly, structural OCT can be used to identify exudation from these vessels. A shortcoming of these imaging modalities is that they are primarily able to identify exudation from CNV rather than the CNV itself. Optical coherence tomographic angiography is not dependent on the presence of vascular leakage, and is therefore able to detect both nonexudative and exudative CNV.

Nonexudative CNV has not been reported as a clinical entity, but does have precedence in the histologic literature. In a post mortem review of a 150 globes with a clinical diagnosis of intermediate AMD, Sarks[17] identified 17 eyes (11%) with histologic evidence of new vessel proliferation. In our small case series of 32 eyes with no clinical signs of exudative AMD, we identified a 6.25% rate of CNV using OCT angiography. The absence of previous clinical reports

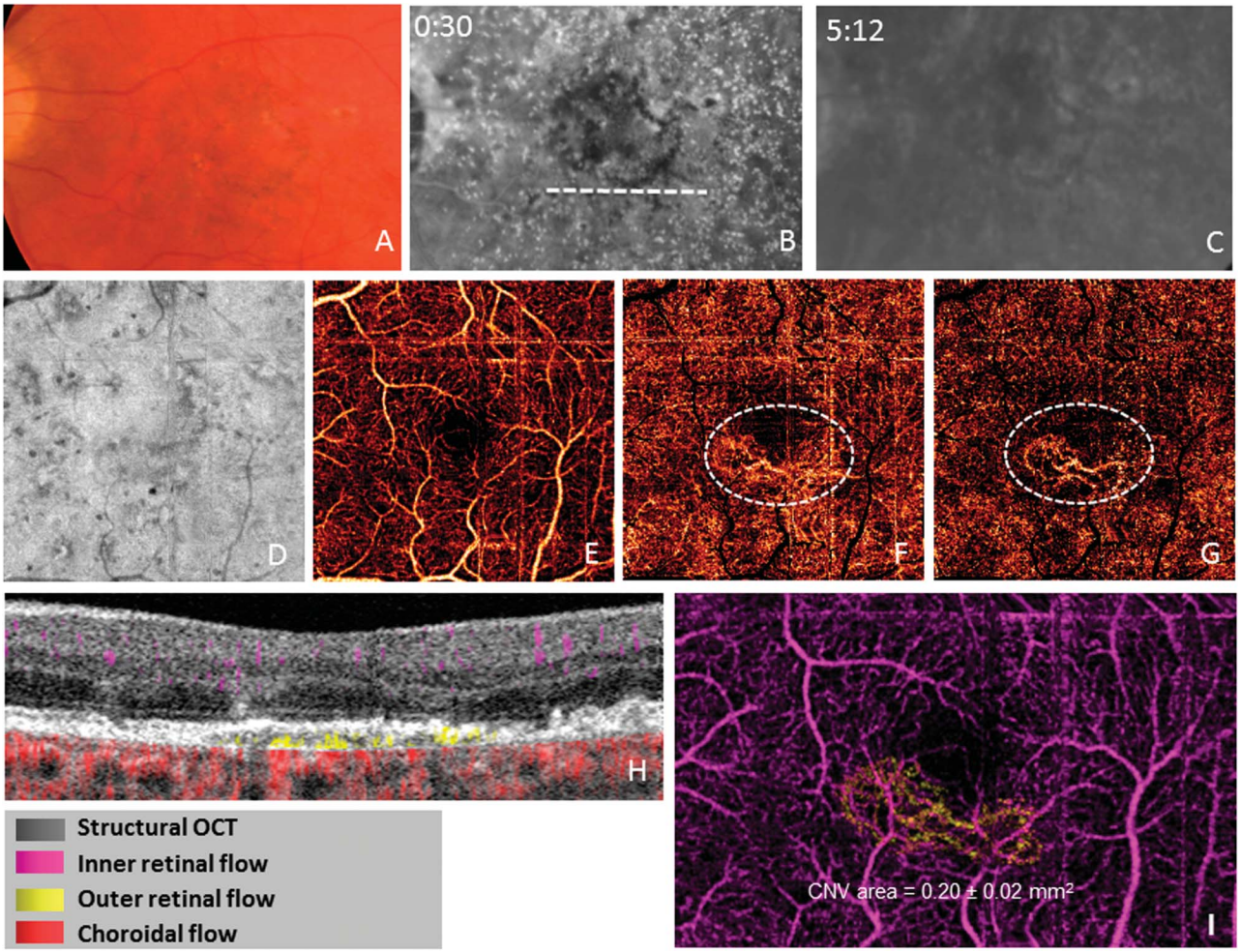

Fig. 3. Case 2 of nonexudative CNV (left eye). **A.** Color photograph. **B** and **C.** Early- and late-phase fluorescein angiograms showing scattered staining of drusen but no dye leakage. **D.** En face structural OCT of the RPE slab. **E.** Inner retinal OCT angiogram. **F.** Outer retinal OCT angiogram with suppressed projection artifact with CNV (white circle). **G.** Choriocapillaris OCT angiogram with CNV (white circle). **H.** Color-coded cross-sectional OCT angiogram (position indicated by a white line on **B**) demonstrating Type I CNV (yellow). **I.** Color composite en face OCT angiogram of retinal vessels (purple) and CNV (yellow). The numbers showed the mean ± SD of the CNV area.

on nonexudative CNV is likely due to the fact that there had not been a good way to identify these lesions by symptoms, clinical examination, FA, or structural OCT.

The relationship between exudative and nonexudative CNV is unknown. At this time, it is uncertain whether one is the predecessor of the other or whether they are two separate clinical entities. Miller et al hypothesized that nonexudative CNV may be a mature form of CNV that has developed competent vessels. They correlated the ultrastructure of experimentally induced CNV with the degree of fluorescein leakage on FA. Leaking subretinal plexi contained fenestrated endothelial walls with intermediate interendothelial cell junctions. The nonleaking vessels maintained fenestrations but developed interendothelial tight junctions.[18] It is possible that nonexudative CNV in our cases detected with OCT angiography may have endothelial tight junctions resulting in an indolent CNV. Conversely, Gass hypothesized that the neovascular networks may initially have low flow with minimal or no exudation. As the CNV develops, flow may increase resulting in exudation.[19]

Longitudinal studies with OCT angiography may help answer the question regarding the natural history of nonexudative CNV. In our study, we were able to longitudinally follow one case of nonexudative CNV (Case 2) with OCT angiography over 8 months. During this time, the visual acuity remained stable and the CNV did not develop exudation on OCT. This absence of vision loss in this case contradicts the natural history of typical exudative CNV lesions associated with AMD, which lead to advanced vision loss over time.[20,21] Some CNV behave in a benign

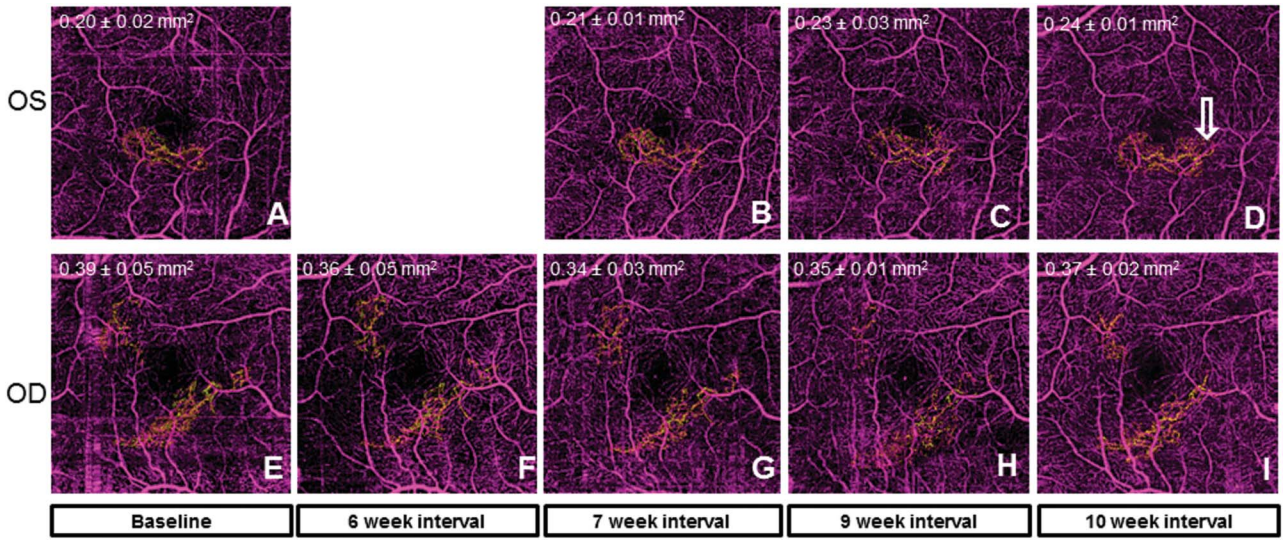

Fig. 4. Serial composite color en face OCT angiograms of Case 2 over 8 months. The time intervals refer to time between treatments of the right eye and imaging of both eyes. **A–D.** Nonexudative CNV (yellow) in the left eye was not treated. Growth of a peripheral CNV branch was evident (arrow). The left eye was not scanned on November 20, 2014. **E–I.** Right eye had exudative CNV treated with intravitreal bevacizumab. Some peripheral CNV branches diminished over time. The numbers showed the mean ± SD of the CNV area.

manner, demonstrating minimal exudation or vision loss over several years. In fact, these have been hypothesized to be compensatory vessels, which may play a protective role in the prevention of RPE atrophy.[16,22] In Case 2, the nonexudative CNV behaved in an indolent fashion over 8 months. Currently, we do not recommend treatment of asymptomatic nonexudative CNV detected with OCT angiography. Given this is the first and only case report with serial follow-up of nonexudative CNV detected with OCT angiography, it is difficult to comment on the natural history of these lesions. Additionally, it is unknown whether anti-VEGF treatment in the fellow eye could alter the natural history.[23] Further studies with larger sample sizes and longer follow-up are needed.

The quantitative metric of the CNV area could be a useful tool to monitor nonexudative CNV growth over time and response to treatment in cases of exudative CNV. In this study, both graders underwent training for CNV area measurement; however, Grader I had more experience measuring the CNV area, which may explain his higher ICC score of 0.99 compared with 0.91. In Case 2, both graders independently identified reductions in the CNV flow area in the right eye undergoing treatment at follow-up visits 2 and 3, which had the shortest intervisit treatment interval. As treatment interval was extended, both graders agreed that the CNV area increased, and at the last visit, the SRF had returned as well. The repeatability and reproducibility of the CNV area seemed adequate to detect clinically significant change in the CNV area over time in both eyes. Recent reports have shown enlarging CNV area, determined with indocyanine green angiography, can predict the development of SRF/IRF.[24,25] Optical coherence tomographic angiography is a novel way to measure the CNV area. Future study is needed to determine whether the CNV area determined by OCT angiography is comparable to that of indocyanine green angiography and whether a change in the CNV area can provide useful information for CNV management.

These cases support the use of OCT angiography in screening AMD patients with a high risk of developing CNV. Optical coherence tomographic angiography can detect both exudative[13] and nonexudative CNV. It is also less invasive than FA and takes less time.

Conclusion

This small case series demonstrates the use of OCT angiography to detect nonexudative CNV not identifiable on FA and structural OCT. Further study is needed to determine the clinical significance of nonexudative CNV, including how often they convert to exudative CNV and at what point treatment may be warranted.

Traditionally, neovascular AMD and exudative AMD are interchangeable terms because they have identical characteristics on FA and structural OCT. Because OCT angiography can now identify nonexudative CNV, we propose that neovascular AMD can now be divided into 2 varieties: exudative neovascular AMD (traditional entity) and nonexudative neovascular AMD (new entity).

Key words: age-related macular degeneration, choroidal neovascularization, diagnostic retinal, imaging, optical coherence tomography angiography.

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