Association of Choroidal Neovascularization and Central Serous Chorioretinopathy With Optical Coherence Tomography Angiography

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IMPORTANCE Choroidal neovascularization (CNV) is a major cause of vision loss in chronic central serous chorioretinopathy (CSCR). Detecting CNV using fluorescein angiography (FA) may be challenging owing to the coexistence of features related to the primary diagnosis of CSCR. Optical coherence tomography angiography (OCTA) allows noninvasive visualization of retinal and choroidal vasculature via motion contrast and may contribute to the unequivocal diagnosis of CNV in this population.

OBJECTIVE To evaluate the sensitivity of spectral-domain OCTA in detecting CNV associated with chronic CSCR.

DESIGN, SETTING, AND PARTICIPANTS Observational cross-sectional study including 23 patients (27 eyes) who presented at the New England Eye Center between August 1, 2014, and November 30, 2014, with suspected CNV complicating chronic CSCR and underwent standard assessment for CNV diagnosis, including FA imaging. Participants were prospectively recruited to receive imaging tests using prototype OCTA software on a commercially available spectral-domain OCT. Orthogonal registration and the merging of 2 consecutive image sets were used to obtain 3 × 3-mm and 6 × 6-mm OCT angiograms centered at the macula. Two independent readers masked to other imaging findings performed a qualitative analysis on OCTA depictions of vascular flow representing CNV and the morphologic appearance of CNV.

MAIN OUTCOMES AND MEASURES Choroidal neovascularization location as well as retinal pigment epithelial detachment internal reflectivity and the presence of subretinal and intraretinal fluid. Sensitivity and specificity of OCTA in detecting CNV were estimated using FA as the standard examination reference.

RESULTS Choroidal neovascularization was diagnosed in 8 of 27 eyes (30%) based on FA imaging analysis. Optical coherence tomography angiography and corresponding OCT B-scans detected 100% (8 of 8) of these CNV lesions and correctly excluded 100% (19 of 19) of eyes with CSCR without CNV. Sensitivity was 100% (95% CI, 0.62-1) and specificity was 100% (95% CI, 0.82-1). Morphologic appearance, location, and position of the CNV relative to the retinal pigment epithelium and Bruch membrane were described using OCTA that combined flow and structural information.

CONCLUSIONS AND RELEVANCE This study suggests that OCT alone (OCTA and coregistered OCT B-scans) features sensitivity and specificity comparable with FA for the detection of CNV in eyes with chronic CSCR.

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choroidal neovascularization (CNV) is a relatively uncommon sequela of chronic central serous chorioretinopathy (CSCR), with incidence estimates ranging from 2% to 9%. Moreover, CNV can be a major cause of reduced visual acuity in long-standing CSCR. It is well known that CNV is more common in certain eyes with CSCR, such as those who have undergone laser photocoagulation, older patients with CSCR, and eyes that feature diffuse retinal pigment epithelium (RPE) loss.

Because of overlap in presentation and findings with active or chronic CSCR, the definitive diagnosis of CNV in CSCR is often challenging. Clinical features suggestive of CNV in CSCR include subretinal and/or sub-RPE hemorrhage, lipid, sub-RPE, subretinal or intraretinal fluid, subretinal hyperreflective material on OCT, and interruptions in the RPE on cross-sectional OCT. However, some of these features are prominently noted in chronic CSCR as well, thereby accounting for possible misdiagnosis. Features that can be seen in both chronic CSCR with and without CNV include retinal pigment epithelial detachment (RPED), subretinal fluid, intraretinal fluid, cystoid macular degeneration, retinal atrophy, and diffuse irregular hyperfluorescence on fluorescein angiography (FA) or indocyanine green angiography. Therefore, an imaging modality that would contribute to the unequivocal diagnosis of CNV in this population would be invaluable.

Optical coherence tomography angiography (OCTA) enables distinct depth-resolved 3-dimensional visualization of the choriocapillaris and retinal microvasculature. The concept underlying OCTA is that in a static eye, the only moving structure in the fundus is blood flowing in the vessels. Optical coherence tomography angiography generates contrast in structure in the fundus is blood flowing in the vessels. Optic coherence tomography angiography provides choroidal perfusion software algorithm within this device generated 3-dimensional 3 × 3 mm and 6 × 6 mm OCT en face images (OCT angiograms). These were generated for each eye by orthogonal registration and the merging of 2 consecutive volumes centered at the macula. Three-dimensional OCT angiograms were coregistered with the cross-sectional OCT B-scans, allowing visualization of both retinal flow and structure in tandem.

Methods

Consecutive patients examined at the New England Eye Center between August 1, 2014, and November 30, 2014, who had the clinical diagnosis of chronic CSCR underwent standard imaging assessment for CNV diagnosis, which encompassed FA and structural OCT, were prospectively offered enrollment in the study. Exclusion criteria included the absence of RPED on standard Cirrus HD-OCT software, version 4.5 (Carl Zeiss Meditec), spectral-domain (SD) OCT, and any associated, previous, or concomitant ophthalmological condition that could confound the interpretation of clinical and imaging findings for the diagnosis of CSCR, such as age-related macular degeneration. The study protocol was approved by the Tufts Medical Center Institutional Review Board. Written informed consent was obtained before OCTA examination in accordance with the Tufts Medical Center Institutional Review Board.

Chronic CSCR was defined as at least 6 months of visual acuity symptoms with documented clinical features of CSCR, including subretinal fluid and RPE changes located at the macular area on dye angiography and SD-OCT imaging. Clinical examination of both eyes and standardized imaging assessment were used to diagnose chronic CSCR and evaluate for associated CNV. Mean subfoveal choroidal thickness was measured on cross-sectional B-scans using standardized SD-OCT.

Eyes were divided into 2 groups based on clinical evaluation and FA. Group 1 eyes (neovascular) demonstrated CNV associated with chronic CSCR diagnosed clinically and by FA while group 2 eyes (non-neovascular) demonstrated chronic CSCR with focal or multiple PEDs without CNV.

Consenting patients were enrolled for imaging using a prototype AngioVue SD-OCT OCTA software (Optovue Inc) within a commercially available Avanti SD-OCT device (Optovue Inc) that operated at 70 000 A-scans per second to acquire OCTA volumes consisting of 304 × 304 A-scans in approximately 2.6 seconds. The split-spectrum amplitude decorrelation angiography software algorithm within this device generated 3-dimensional 3 × 3 mm and 6 × 6 mm OCT en face images (OCT angiograms). These were generated for each eye by orthogonal registration and the merging of 2 consecutive volumes centered at the macula. Three-dimensional OCT angiograms were coregistered with the cross-sectional OCT B-scans, allowing visualization of both retinal flow and structure in tandem.
OCT images of eyes with an RPED secondary to chronic CSCR were evaluated for possible CNV. Three-dimensional OCT angiograms were coregistered with the cross-sectional OCT B-scans, allowing visualization of both retinal flow and structure in tandem. The OCT images of eyes with RPED secondary to chronic CSCR were evaluated for possible CNV. The OCT software was used to manually alter the automated segmentation and its relative depth in the retina and choroid. Two automated segmentation lines referencing the outer retina on coregistered OCT B-scans were manually fine-tuned to be located at the outer border of the outer plexiform layer (inner boundary) and the level of the Bruch membrane (outer boundary). In healthy eyes, this segmentation involving the outer retina is not expected to have any vascular structures and, thus, OCTA is not expected to identify blood flow. Therefore, CNV was defined as evidence of a decorrelation signal at the outer-retina level on OCTA consistent with the vascular component of the lesion.

Choroidal neovascularization subtypes were determined on coregistered OCT B-scans as type 1 CNV if domed elevation of the RPE layer with sub-RPE material of mixed reflectivity was present\textsuperscript{12,13} and as a mixed variant of type 1 and type 2 CNV if a hyperreflective structure anterior to an elevated disrupted RPE approximation to the binomial distribution.

The inner and outer boundaries of OCT angiograms included all apparent CNV vessels. The prototype software did not allow the segmentation curvature of the inner or outer boundaries lines to be corrected, only allowing movements up or down on the OCT B-scan using the original automated segmentation line course. An artifact removal toggle function in the software was used to subtract the retinal vessel shadowing from the en face flow image.

Two independent and trained readers from the Boston Image Reading Center (M.A.B.F. and T.E.D.C.) who were masked to other imaging findings evaluated the en face sectioning OCTA images and coregistered OCT B-scans for the following features: evidence of vascular flow above the Bruch membrane at the level of the outer retina representing CNV, CNV appearance, RPED internal reflectivity, subretinal fluid, and intraretinal fluid. The appearance of CNV on OCTA was characterized as either well-circumscribed (lacy wheel or sea fan–shaped vessels) or poorly circumscribed (long filamentous vessels). The RPED internal reflectivity was determined to be either hyperreflective or hyporeflective, with internal reflectivity that could be either heterogeneous or homogeneous. Subretinal fluid and intraretinal fluid was determined to be present or absent using the correlating OCT B-scans. The FA and OCTA examinations were evaluated to estimate the sensitivity and specificity of OCTA in detecting CNV, using FA as the reference standard. For sensitivity and specificity, 95% CIs were calculated by normal approximation to the binomial distribution.

Results

Twenty-seven eyes of 23 patients with consecutive CSCR demonstrated as chronic CSCR and associated RPED were enrolled in this study. Three patients (3 eyes) that presented with subretinal fluid but no findings of RPED via coregistered B-scans were excluded from the study. The baseline characteristics were as follows: 15 of 23 patients were male (65.2%), 21 of 23 were white (91.3%), and 2 of 23 patients were Asian (8.7%), with a mean (SD) age of 50.9 (13.9) years. Mean (SD) subfoveal choroidal thickness measured on standard OCT B-scans was 414.9 (71.1) μm, which was thicker than the mean choroidal thickness determined by SD-OCT previously reported for healthy participants between their fourth and fifth decades of life (287 [76] μm\textsuperscript{15} and 272 [81] μm\textsuperscript{16}).

Eight of 27 eyes (30%) demonstrated definite CNV on clinical examination and FA and were included as group 1 (neovascular chronic CSCR). In this group, 4 eyes had FA and indocyanine green angiography performed, 2 eyes had only FA, and 2 eyes received only standard SD-OCT on the same day as the OCTA but FA at 12 weeks preceding the OCTA in 1 eye and 3 weeks in the other. Dye-based angiography showed clear evidence of CNV in all group 1 eyes. Of these, 3 eyes received no treatment prior to enrollment, 1 eye was treated with a single session of full-time photodynamic therapy (PDT), 1 eye was treated with 2 sessions of full-time PDT for CSCR, 1 eye was treated with laser photoacoagulation and a single session of full-time PDT for CSCR, 1 eye was treated with intravitreal anti-vascular endothelial growth factor therapy for CNV, and 1 eye received focal laser, 1 session of half-time PDT and 2 sessions of full-time PDT, and micropulse laser for CSCR and intravitreal anti-vascular endothelial growth factor therapy for CNV 2 months to 12 years prior to enrollment in the study.

Nineteen of 27 eyes did not demonstrate CNV on clinical examination or FA and were classified as group 2 (non-neovascular chronic CSCR). Ten eyes had both FA and indocyanine green angiography, 4 eyes had only FA, and 5 eyes had standard SD-OCT on the same day as OCTA but FA within 24 weeks preceding the OCTA. In this group, all eyes imaged with dye-based angiography showed no evidence of CNV. Fourteen eyes received no treatment prior to enrollment, 2 eyes were treated with a single session of full-time PDT, 1 eye received a single session of half-time PDT, 1 eye was treated with a single session of full-time PDT session and intravitreal anti-vascular endothelial growth factor therapy, and 1 eye received laser photoacoagulation and a single session of full-time PDT for CSCR 2 months to 4 years prior to enrollment.

Two trained readers at the Boston Image Reading Center who were masked to other imaging findings determined that 8 of 8 eyes (100%) from group 1 and 0 of 19 eyes from group 2 had CNV on OCTA using the split-spectrum amplitude decorrelation angiography algorithm on the prototype OCTA software. Of all confirmed CNV cases, 4 of 8 eyes (50%) had type 1 CNV and 4 of 8 eyes (50%) had type 1 and type 2 mixed-variant CNV detected by both standard OCT and corresponding OCTA B-scans. Thus, there was complete agreement between the results obtained by OCTA and multimodal evaluation for all eyes in both groups. The specificity for the detection of CNV using OCTA was 100% (95% CI, 0.82-1) with a sensitivity of 100% (95% CI, 0.62-1). Positive and negative predictive values were 100%.

From the 8 eyes with confirmed CNV (group 1), 5 eyes had well-circumscribed vessels in the CNV area and 3 eyes showed poorly circumscribed vessels on OCTA (Figure 1). Manual displacement of the outer boundary segmentation line down to
the choriocapillaris level on correlating OCT B-scans was performed (Figure 2) and allowed delineation of CNV boundaries in 6 of 8 eyes (75%) and the feeder vessel in 2 of 8 eyes (25%) with CNV (Figure 2 and Figure 3). In 2 eyes that were previously treated with 2 or more PDT sessions and presented with poorly circumscribed vessels on OCTA, manual adjustment of segmentation level to the choriocapillaris was unable to correct delineate the boundaries of the CNV complex (Figure 4). Six of 8 eyes (75%) with CNV presented with subretinal fluid and 2 of 8 eyes (25%) presented with both intraretinal and subretinal fluid on corresponding OCT B-scans. All eyes with CNV presented with domed elevation of the RPE and heterogeneous hyperreflective content under the RPE line.

All 19 eyes without CNV (group 2) had RPED identified on coregistered OCT B-scans. In this group, 15 of 19 eyes (78.9%) had subretinal fluid, 1 of 19 eyes (5.3%) had intraretinal fluid, and 3 of 19 eyes (15.8%) had no findings of subretinal or intraretinal fluid on corresponding B-scans. Nine of 19 eyes (47.4%) had domed elevations of the RPE layer with heterogeneous and hyperreflective content and 10 of 19 eyes (52.6%) had homogeneous and hyporeflective content under the RPE line (Figure 5).

Discussion
Dye-based angiography is the current standard to diagnose CNV. However, detecting secondary CNV in patients with CSCR using these imaging modalities may be challenging owing to the coexistence of clinical, OCT, and angiographic findings related to the primary diagnosis of CSCR, including subretinal fluid, in-
traretinal cystic changes, diffuse RPE loss resulting in widespread window defects on FA, scattered points of RPE leakage, RPEDs, and multifocal patchy hyperfluorescence of the inner choroid seen on indocyanine green angiography.\textsuperscript{3,6}

Ferrara et al\textsuperscript{18} reported OCT findings in 2 eyes with CNV secondary to CSCR using structural en face swept-source OCT images. They reported focal and diffuse vascular dilation at the level of the choriocapillaris. However, corresponding multimodal analysis and 3-dimensional OCT visualization suggested that some of the features may be related to pronounced choroidal vascular dilatation or remodeling or extracellular fluid accumulation associated with CSCR rather than specific to CNV.

Yamamoto\textsuperscript{19} measured blood flow velocity in feeder vessels and demonstrated that blood flow resistance increases and blood flow velocity decreases in CNV microcirculation, particularly in smaller CNVs. Jia et al\textsuperscript{11} obtained quantitative information regarding CNV in patients with age-related macular degeneration, showing CNV flow and area in 5 eyes using a swept-source OCT angiography system with a split-spectrum amplitude decorrelation angiography algorithm and detected a higher flow index of CNV in eyes with larger CNVs, those that were type 2 compared with type 1, and combined CNVs. Spectral-domain OCT has lower imaging speeds compared with swept-source OCT, with a higher sensitivity roll-off with imaging depth. However, in our study, limitations of SD-OCT technology did not affect successful visualization of blood flow inside the CNV network in all eyes, regardless of the type and size of the CNV, as OCTA successfully distinguished CNV from the surrounding outer retinal tissue and nonflow material with RPED.

We identified CNV and determined the position of the CNV relative to the RPE and Bruch membrane by using OCTA that combined flow (OCT angiograms) and structural information (coregistered OCT B-scans). This supports previous findings using the split-spectrum amplitude decorrelation angiography OCTA technique in evaluating CNV and monitoring morphologic features for treatment and follow-up.\textsuperscript{11} Further-
more, because the OCTA image is depth-resolved, manual adjustment of the segmentation level at the outer boundary of the outer retina slightly posterior to the Bruch membrane allowed tomographic visualization of feeder vessels between

Figure 3. Feeder Vessel and Choroidal Neovascularization After Manual Adjustment of the Outer Boundary on a Coregistered B-Scan

Figure 4. Inability in Delineating Margins of Choroidal Neovascularization on Optical Coherence Tomography Angiography

Fluorescein angiography (A) and an optical coherence tomography angiogram (B) show choroidal neovascularization. Optical coherence tomography angiography with manual adjustment of the outer red segmentation line shows larger choroidal neovascularization and the feeder vessel (arrowhead) originating from the scar area (C). B-scans for panels B (D) and C (E).

Optical coherence tomography angiography of an eye previously treated with photodynamic therapy for choroidal neovascularization. A and B, Automated segmentation at the outer retinal level shows large and poorly circumscribed choroidal neovascularization. C and D, Manual adjustment of the segmentation lines was unable to accurately identify margins of the choroidal neovascularization.
the choroid and the CNV in 2 eyes, which is rarely possible to identify using angiography.

Except for 2 eyes that were previously treated with PDT sessions, delineation of the CNV boundaries was achieved by performing a manual adjustment of the outer segmentation line. Long-term effects of PDT, such as choroidal vascular remodeling, RPE disturbance, enlargement of CNV membranes, recanalization of occluded vessels, and choriocapillary occlusion,

may limit accurate determination of CNV size in such eyes. However, it did not affect the identification of CNV in this study. This study was limited by a relatively small number of patients and the inability to manually correct automatically detected segmentation curves, which limited the suppression of choriocapillaris artifact in the en face sectioning of the outer retina. However, high sensitivity and specificity of detection of CNV in this small case series was achieved. There were several reasons for high sensitivity and specificity. Because CNV in CSCR is rarely associated with the massive subretinal hemorrhage that limits penetration of OCT signal, CSCR-associated CNV may be particularly suited to being identified on OCTA. In a similar case series performed on a mixed group of patients with CNV that included CNV secondary to wet age-related macular degeneration, the sensitivity of OCTA in detecting CNV was much lower, at approximately 50% (T. E. de Carlo, BS, unpublished data, 2015). Moreover, readers evaluating OCTA in this study were highly trained and performed a dynamic evaluation of OCTA volume, altering the segmentation lines when needed. Such an evaluation maximizes the sensitivity and specificity of detection of CNV on OCTA because accurate automated segmentation is often difficult in eyes with

Absant abnormal vascular flow and the presence of well-circumscribed areas without an optical coherence tomography signal suggest shadowing artifacts in the presence of retinal pigment epithelial detachment. Coregistered B-scans show different retinal pigment epithelial detachment reflectivities. A, Retinal pigment epithelial detachment with homogeneous hyporeflectivity. B-D, Retinal pigment epithelial detachment with heterogenous hyperreflectivity. Asterisks indicate the locations of pigment epithelial detachment on the respective optical coherence tomography angiograms.
Conclusions
We demonstrated an association between noninvasive OCTA and dye-based angiography in detecting CNV associated with chronic CSCR. This study suggests that OCTA alone (OCTA and registered OCT B-scans) features sensitivity and specificity comparable with FA imaging for the detection of CNV in eyes with chronic CSCR and may be a viable alternative to dye-based angiography in the diagnosis of CNV in these patients. Because OCTA is a completely noninvasive test, it could be considered a first step in identifying CNV in CSCR. Future studies with larger sample sizes are needed to improve our understanding of this diagnostic method and provide further information to validate this imaging technique in clinical practice.