AMERICAN ACADEMY OF OPHTHALMOLOGY®

Morphologic Predictors and Temporal Characteristics of Conversion from Nonexudative to Exudative Age-Related Macular Degeneration in the Fellow Eye

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Purpose: To describe the systemic and ocular features of fellow eyes' association with nonexudative neovascularization (NV) based on OCT angiography (OCTA) and to identify longitudinal morphologic changes associated with progression to exudation.

Design: Cohort study of contralateral eye in patients with neovascular age-related macular degeneration (nAMD) in 1 eye.

Participants: Patients with nAMD in one eye were eligble for inclusion and enrolled between June 2015 and Jan 2017. The study eye was the contralateral eye that was free of nAMD with a minimum follow-up of 1 year.

Methods: Progressive multimodal imaging was performed on both eyes. Nonexudative NV was detected on OCTA in the study eye and quantitative changes analyzed. Nonexudative NV eyes were divided into progression to exudation or not during a minimum of 12 months follow-up.

Main Outcome Measures: Association between systemic and ocular characteristics with nonexudative NV were determined. Change in OCTA size, vessel density, and vessel length density were compared between visits as predictors of progression to exudation.

Results: Among 229 study eyes, 21 (9.1%) had nonexudative NV detected on OCTA at baseline. Hyperlipidemia (adjusted odds ratio [AOR], 1.3; 95% confidence interval [CI], 1.10−3.20; $P = 0.04$), triglycerides (AOR, 2.84 per mmol/L; 95% CI, 1.06−4.35 per mmol/L; $P = 0.02$), and baseline lesion size in the presenting eye (AOR, 1.6 per 500 μm; 95% CI, 1.21−3.25 per 500 μm; $P = 0.03$) were associated significantly with nonexudative NV in the study eye. In the study eye nonexudative NV group, 8 (38%) progressed to exudation, with a mean time to exudation of 377 ± 138 days. The progressor group had larger baseline NV size (1834 ± 552.8 μm vs. 910 ± 461.7 μm; $P < 0.01$), higher increase in vessel density/year (8.3 ± 4.1%/year vs. 1.1 ± 2.5%/year; $P \leq 0.01$), and higher increase in vessel length density/year (15.6 ± 10.6% vs. 1.9 ± 3.6%; $P = 0.02$). The change in lesion size per year was similar in both groups.

Conclusions: Patients with nonexudative NV in the study eye had significant differences in ocular and systemic characteristics. More than a third of study eyes with nonexudative NV at baseline progressed to exudation, suggesting that close monitoring is essential. OCT angiography features associated with exudation include a larger baseline lesion size, increase in vessel density, and vessel length density. *Ophthalmology Retina 2021;5:126-140 © 2020 by the American Academy of Ophthalmology*

Supplemental material available at www.ophthalmologyretina.org.

Neovascular age-related macular degeneration (nAMD) is a major cause of vision loss worldwide.[1−3] This vision loss is a result of significant alterations of macular anatomy features in part because of the exudation resulting from neovascularization. It is well established that these neovascularizations can be present before exudation, and this subclinical phase in nAMD is termed *nonexudative neovascularization*.[4] Nonexudative neovascularization has been described previously in postmortem specimens as neovascular nets in the subretinal pigment epithelial and intrachoroidal spaces.[5,6] These nonexudative neovascularizations also can be observed clinically as late-staining plaques on indocyanine green angiography.[7,8] The detection of nonexudative neovascularization has been improved significantly with the advent of OCT angiography (OCTA), which has led to improved detection and understanding of this entity.[4,9−13]

A few previous studies have reported longitudinal data on nonexudative neovascularization related to the risk of progression to exudation, and most are limited by their small

https://doi.org/10.1016/j.oret.2020.07.005
ISSN 2468-6530/20

sample size.[4,14,15] Currently, no established guidelines exist for follow-up and management of nonexudative lesions because no data exist on the proportion of such lesions that will progress to exudation, nor do data exist on the duration of progression-free intervals. The identification of features on OCTA that may help to predict the progression to exudative nAMD therefore is of importance, and the characterization of such biomarkers can inform monitoring strategies in patients with nAMD in the first presenting eye.[16–20]

We previously reported that approximately 1 in 5 patients with unilateral exudative nAMD have nonexudative neovascularization in the fellow eye[12] and that the presence of nonexudative neovascularization predisposes patients to the development of exudative changes.[13] In the present analysis, we described the longitudinal findings in 229 consecutively enrolled patients with nAMD in 1 eye whose fellow eyes were free of exudation at enrolment and were designated as the study eye. Herein we report (1) the systemic and ocular characteristics showing association with the presence of nonexudative neovascularization in study eyes and (2) risk factors for progression to exudation in study eyes with nonexudative neovascularization.

Methods

Patient Selection

This study was approved by the Singhealth Centralized Institutional Review Board and was conducted according to the tenets of the Declaration of Helsinki. Written consent was provided by all patients for this study. Data were obtained from an ongoing prospective AMD phenotyping study performed at the Singapore National Eye Centre. The detailed methods have been published previously.[12,13,21,22] Consecutive patients with new-onset exudative nAMD who were seen between June 2015 and January 2017 were enrolled, and the study eyes were the contralateral eye that was free of exudative AMD at enrollment. Any subtype of exudative nAMD in the first eye was allowed. Patients with bilateral exudative nAMD were excluded. Based on baseline OCTA findings, study eyes were divided into 2 groups: those with nonexudative neovascularization and those without any features of nonexudative neovascularization. All patients had a minimum of 12 months of follow-up. During follow-up, study eyes were divided further into those that progressed to exudative nAMD (progressor group) and those that did not (nonprogressor group).

Systemic Examination

All patients underwent a full clinical examination and laboratory tests following standardized protocols as described elsewhere.[23–25] A detailed interviewer-administrated questionnaire was used to collect information about medical history, cigarette smoking (defined as current, past, and never), and current medication use. Hypertension was defined as systolic blood pressure of 140 mmHg or more, diastolic blood pressure of 90 mmHg or more, or a physician's diagnosis. Diabetes mellitus was defined as the finding of a random glucose level of 11.1 mmol/L or more or self-reported history of diabetes and use of diabetic medication. Hyperlipidemia was present if self-reported, if the patient reported the use of statins, or both.

Genome-Wide Association Study and Single Nucleotide Polymorphism Selection

We extracted DNA from venous blood samples from all participants. Genotyping was performed using Illumina Human OmniExpress (Illumina, San Diego, CA) or Human Hap610-Quad Beadchip (Illumina, San Diego, CA). For the current analysis, we included 2 major AMD-associated single nucleotide polymorphisms, rs800292 from *CFH* and rs10490924 from *ARMS2*.[26–28]

Multimodal Imaging Acquisition

All eyes underwent 45° color fundus photography (CFP) and spectral-domain (SD) OCT scans with the enhanced depth imaging mode enabled over a 25-line scan, with each line averaged over 9 scans (Heidelberg Spectralis; Heidelberg Engineering, Heidelberg, Germany). OCT angiography was performed on the Heidelberg Retinal Angiograph platform (HRA-C/HRA2/HRA Spectralis; Heidelberg Engineering).

Image Analysis: Color Fundus Photography, Spectral-Domain OCT, and OCT Angiography

Analysis and comparisons of the entire imaging set including CFP, fluorescein angiography (FA), indocyanine green angiography, and spectral-domain OCT were conducted. Drusen on CFP were graded as present or absent and, if present, were graded further according to subtype on CFP and OCT: soft drusen, diameter ≥65 μm; pachydrusen, isolated or scattered yellow-white deposits corresponding to homogenous sub−retinal pigment epithelium material on OCT; and pseudodrusen, 10 or more discrete subretinal accumulations of material present that correspond to whitish deposits on CFP and corresponding hyperreflective mounds above the retinal pigment epithelium as detected on OCT.[29]

Lesion subtype in the first or presenting eye was diagnosed by the treating physician using multimodal imaging and classified further angiographically following criteria from published literature.[30–32] The lesion characteristics reported herein are correlated to the new Consensus on Neovascular Age-Related Macular Nomenclature for Reporting group criteria.[33] The nonexudative nature was confirmed by the lack of leakage on FA and absence of intraretinal or subretinal fluid on cross-sectional OCT. All nonexudative neovascularization identified on OCTA appeared as a hyperfluorescent plaque on mid- to late-phase indocyanine green angiography images.[8]

The greatest linear diameter (GLD) of the exudative nAMD lesion in the presenting eye was measured on FA. This was measured taking into account the size of the neovascularization including any hypofluorescence from blood or a serous detachment of the retinal pigment epithelium contiguous with the neovascularization. Cross-sectional spectral-domain OCT through the fovea was used to measure subfoveal choroidal thickness and was defined as the distance between the outer limits of Bruch's' membrane to the choroid−scleral interface. All measurements were made using the calliper tool provided in the Heidelberg explorer software. During follow-up, new-onset subretinal fluid, intraretinal fluid, or both were used to classify eyes from nonexudative to exudative AMD. Based on these definitions, we placed participants into 2 groups: (1) the progressor group, which included study eyes that converted to exudative nAMD, and (2) the nonprogressor group, which included eyes that did not demonstrate exudation over the course of follow-up as defined previously. All features that were graded and definitions are included in Supplemental Table 1 (available at www.ophthalmologyretina.org).

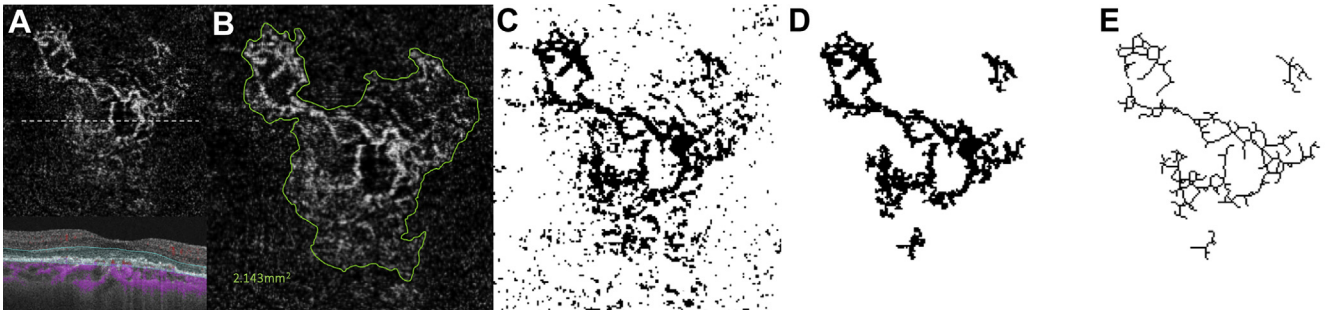

Figure 1. Processing of OCT angiography images for quantitative measurements. **A**, Original en face image of choroidal neovascularization with corresponding B scan (inset, dotted line) obtained at the level of the outer retina (basement membrane to 70 μm below the inner plexiform inner nuclear layer border). **B**, En face image imported into ImageJ, with the size of the lesion measured by manually segmenting the lesion (green outline). **C**, Binarized image using the Otsu method. **D**, Binarized image using the Otsu method with attribution filtering applied to remove outliers to measure the vessel density. **E**, Lesion image further skeletonized to measure the vessel length density.

OCT Angiography Acquisition

Swept-source OCTA was performed using the Topcon DRI OCT Triton (Topcon, Tokyo, Japan), which uses a 1050-nm light source and a scan speed of 100 000 A scans per second. Angiographic images were analyzed by the fully automated OCT Angiography Ratio Analysis algorithm provided by the manufacturer, which is based on an intensity ratio analysis without requiring splitting the spectrum, thus preserving the axial resolution. Only high-quality OCTA scans were analyzed (image quality, >45). All patients had at least 2 high-quality OCTA scans, and 3 scans from 3 patients were rejected. The presence or absence of nonexudative neovascularization was determined based on OCTA, specifically detected on the outer retinal slab. The outer retinal slab (defined as a slab 70 μm below the junction between the inner plexiform layer and inner nuclear layer to Bruch's membrane) was identified using inbuilt software. The boundaries of the retinal slab were adjusted for optimum visualization of the neovascular complex. This modified slab was exported to ImageJ (National Institutes of Health, Bethesda, MD). Image analysis on this slab is outlined below. In addition, because aneurysmal lesions often are located in a plane more anterior to the neovascularization, a 50-μm thick slab with anterior border on the base of the retinal pigment epithelium line was used to visualize aneurysmal lesions.

OCT Angiography Quantitative Analysis of Nonexudative Neovascularization

Image J software was used for all image processing and quantification (Fig 1). The area and greatest linear dimension were obtained by manually outlining the margins of the nonexudative neovascularization lesion using the en face image at each visit. The change in lesion size per year was calculated by dividing the difference in area from baseline to final visit by the interval between visits in years.

Vessel density (VD) and vessel length density (VLD) were determined for each lesion imaged on OCTA. To quantify VD and VLD, images were binarized by the Otsu method (specification of this algorithm can be found online: https://imagej.net/Auto_Threshold). Briefly, this method is an adaptive thresholding algorithm for image binarization. An optimal threshold value is calculated and evaluated by between-class variance (or within-class variance). Binarized images underwent attribute filtering (grayscale attribute filtering[34] with opening attribute set to a minimum area of 50 and connectivity at 4) to remove noise and outliers.

Vessel density is expressed as the ratio of white pixels (i.e., the lesion) to the total pixels within the manually segmented lesion (percent). Change in VD per year was calculated subsequently by dividing the difference between follow-up VD and baseline VD by interval (percent per year).

Vessel length density, defined as a ratio of vessel length per area, was derived by skeletonizing the binarized image used for VD and dividing the sum of the length of skeletonized vessels (pixels) by total pixels within the segmented lesion (percent). Similarly, VLD per year was calculated by dividing the difference between follow-up VLD and baseline VLD by interval (percent per year).

Quantifying Interscan Variation in Lesion Size, Vessel Density, and Vessel Length Density

To ascertain the interscan variation in the aforementioned measures (lesion size, VD, and VLD), analysis of 2 consecutive, high-quality OCTA acquisitions (>45) at the same sitting were performed in 5 eyes independent of this cohort. Mean change in lesion size, VD, and VLD was measured between both scans, and the proportion change between each scan of the same eye of each of the 3 measures was calculated. The mean proportion variation when comparing consecutive, repeat OCTA performed on 5 eyes at the same sitting was 6.5% for lesion size, 5.5% for VD, and 5.7% for VLD. A value larger than these mean changes for each measure was considered significant when comparing longitudinal scans.

Statistical Analysis

Descriptive data are presented as mean (SD) and number (percent). Risk factors were classified as binary traits (e.g., diabetes: yes or no) or as continuous variables (e.g., age). Generalized estimating equations were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), unadjusted and adjusted for confounding risk factors such as age and gender associated with nonexudative neovascularization and progression to exudation (progressor group). In multivariate analyses, only those variables that reached significance in the univariate analyses were included in the model. A P value of 0.05 or less was considered statistically significant. All analyses were calculated

Table 1. Characteristics of Patients with and without Nonexudative Neovascularization at Baseline

Characteristics	Nonexudative Neovascularization		P Value
	Absent (n = 208)	*Present (n = 21)*	
Age (per year), mean ± SD	70.4 ± 9.2	67.2 ± 8.6	0.23
Female gender, no. (%)	99 (47.6)	11 (52.4)	0.5
Ethnicity, no. (%)			
Chinese	162 (77.8)	16 (76.2)	0.97
Malay	21 (10.1)	2 (9.5)	
Indian	17 (8.1)	2 (9.5)	
Others	8 (3.8)	1 (4.8)	
BMI, no. (%)			
Underweight	8 (4)	2 (10)	0.41
Normal	107 (51.2)	15 (70)	
Overweight	74 (35.8)	4 (20)	
Obese	19 (8.9)	0 (0)	
Smoking, no. (%)	42 (20.2)	9 (42.9)	**0.04**
Diabetes, no. (%)	21 (10.1)	1 (4.8)	0.28
Hypertension, no. (%)	82 (39.4)	12 (57.1)	0.07
Hyperlipidemia, no. (%)	95 (45.7)	14 (66.7)	**0.03**
Angina, no. (%)	10 (4.8)	0 (0)	0.34
Myocardial infarction, no. (%)	14 (6.7)	0 (0)	0.26
Stroke, no. (%)	12 (5.8)	1 (4.8)	0.98
HbA1c (%), mean ± SD	5.9 ± 0.9	5.6 ± 0.4	0.38
Cholesterol (mmol/L), mean ± SD	5.3 ± 1.2	5.9 ± 0.8	**0.04**
HDL (mmol/L), mean ± SD	1.5 ± 0.3	1.6 ± 0.4	0.2
Triglycerides (mmol/L), mean ± SD	1.7 ± 0.7	2.1 ± 0.4	**0.03**
LDL (mmol/L), mean ± SD	3.5 ± 0.9	3.8 ± 0.8	0.13
Cholesterol-to-HDL ratio	3.8 ± 0.9	3.7 ± 0.9	0.8
Statin use, no. (%)	53 (25.4)	4 (19.0)	0.54
Baseline VA (first eye; letters), mean ± SD	55.8 ± 13.2	47.3 ± 14.5	0.06
Baseline GLD (first eye; μm), mean ± SD	3763 ± 1252	4577 ± 1020	**0.02**
Lesion type (first eye), no. (%)			
PCV	102 (49)	7 (33.3)	0.69
Type 1 MNV	82 (39.4)	11 (52.4)	
Type 2 MNV	21 (10.2)	3 (14.3)	
Type 3 MNV	3 (1.4)	0 (0)	
Drusen type (study eye), no. (%)			
None	65 (31.3)	8 (35.7)	0.74
Pachydrusen	54 (26.1)	6 (28.5)	
Pseudodrusen	11 (5.2)	0 (0)	
Soft	67 (32.2)	6 (28.6)	
Soft + pachydrusen	5 (2.6)	2 (7.1)	
Soft + pseudodrusen	5 (2.6)	0 (0)	
Genotype, no. (%)			
CFH_rs800292_G (any risk allele present)	162 (77.8)	19 (90.5)	0.06
ARMS_rs10490924_T (any risk allele present)	149 (84.2)	16 (76.257)	0.60
CFH_rs800292_G and ARMS_rs10490924_T (all 4 risk alleles present)	46 (22.1)	8 (38.1)	0.07

BMI = body mass index; CFH = complement factor H; GLD = greatest linear diameter; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MNV = macular neovascularization; PCV = polypoidal choroidal vasculopathy; SD = standard deviation; VA = visual acuity.

using R Statistical Analysis (R Foundation for Statistical Computing, Vienna, Austria).[35]

Results

Among 229 consecutive patients with unilateral exudative nAMD, 21 eyes (9.1%) demonstrated nonexudative neovascularization in the fellow eye. Patient and ocular characteristics of participants without nonexudative neovascularization and those with nonexudative neovascularization are shown in Table 1.

Comparison of Demographic and Systemic Characteristics of Participants with Study Eyes without Nonexudative Neovascularization (n = 208) versus Those with Nonexudative Neovascularization (n = 21)

The mean age was similar between the 2 groups (70.4 years vs. 67.2 years; $P = 0.23$), as was the proportion of patients who were women (47.6% vs. 52.4%; $P = 0.50$). Also, no difference was found in the ethnicity distribution between groups (Chinese, 77.8% vs. 76.2%; Malay, 10.1% vs. 9.5%; Indian, 8.1% vs. 9.5%; and

Table 2. Risk Factors for Presence of Nonexudative Neovascularization

Characteristics	Nonexudative Neovascularization			
	Odds Ratio (95% Confidence Interval)	*P Value*	*Adjusted Odds Ratio (95% Confidence Interval)**	*P Value*
Age (per yr)	0.96 (0.89–1.04)	0.31		
Female gender	1.7 (0.95–1.46)	0.14		
Ethnicity				
Chinese	Reference			
Malay	1.2 (0.25–5.67)	0.97		
Indian	1.03 (0.22–4.82)	0.81		
Others	1.35 (0.16–11.53)	0.78		
BMI				
Underweight	0.53 (0.06–5.46)	0.31		
Normal	Reference			
Overweight	0.23 (0.02–2.98)	0.26		
Obese	0 (0–infinity)	0.99		
Smoking	2.65 (1.02–6.9)	0.04	1 (0.99–1.0)	0.99
Diabetes	0.33 (0.04–2.71)	0.3		
Hypertension	1.45 (0.89–2.36)	0.13		
Hyperlipidemia	2.32 (1.11–5.93)	0.02	1.3 (1.10–3.2)	0.04
Angina	0 (0–infinity)	0.99		
Myocardial infarction	0 (0–infinity)	0.99		
Stroke	1.03 (0.12–8.82)	0.98		
HbA1c (%)	0.54 (0.19–1.57)	0.26		
Cholesterol (mmol/L)	1.55 (1.1–2.36)	0.03	1 (0.39–2.61)	0.99
HDL (mmol/L)	4.37 (0.72–16.33)	0.11		
Triglycerides (mmol/L)	1.91 (1.21–3.83)	0.02	2.84 (1.06–4.35)	0.02
LDL (mmol/L)	1.45 (0.75–2.82)	0.27		
Cholesterol-to-HDL ratio	0.98 (0.49–1.95)	0.95		
First eye baseline VA (letters)	0.91 (0.79–1.05)	0.18		
First eye baseline GLD (500 μm)	1.33 (1.04–1.71)	0.02	1.6 (1.2–3.2)	0.03
First eye lesion type				
PCV	Reference			
Type 1 MNV	1.8 (0.4–4.15)	0.45		
Type 2 MNV	3.3 (0.31–5.39)	0.32		
Type 3 MNV	0 (0–infinity)	0.99		
Drusen (study eye)				
None	Reference			
Presence	1.87 (0.71–4.9)	0.2		
Pachydrusen	1.89 (0.44–8.15)	0.39		
Pseudodrusen	0 (0–infinity)	0.99		
Soft	1.09 (0.26–4.53)	0.91		
Soft + pachydrusen	3.14 (0.29–8.42)	0.35		
Soft + pseudodrusen	0 (0–infinity)	0.99		
Genotype				
No risk alleles present	Reference			
CFH_rs800292_G (any risk allele present)	1.26 (0.06–1.98)	0.08		
ARMS_rs10490924_T (any risk allele present)	1.5 (0.33–6.90)	0.61		
CFH_rs800292_G and RMS_rs10490924_T (all 4 risk alleles present)	2.36 (0.91–6.12)	0.08		

BMI = body mass index; CFH = complement factor H; GLD = greatest linear diameter; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MNV = macular neovascularization; PCV = polypoidal choroidal vasculopathy; VA = visual acuity.
*Adjusted for age, gender, baseline GLD, smoking status, hyperlipidemia, cholesterol, and triglyceride level.

others, 3.8% vs. 4.8%; $P = 0.97$). Never smokers were less likely to exhibit nonexudative neovascularization (20.2% vs. 42.9%; $P = 0.04$). Those without hyperlipemia also were less likely to have no features of nonexudative neovascularization (45.7% vs. 66.7%; $P = 0.03$). Patients without nonexudative neovascularization demonstrated lower cholesterol levels (5.3 ± 1.2 mmol/L vs. 5.9 ± 0.8 mmol/L; $P = 0.04$) and lower triglyceride levels (1.7 ± 0.7 mmol/L vs. 2.1 ± 0.4 mmol/L; $P = 0.03$). More patients who were homozygous for both AMD risk alleles (CFH_rs800292_G and ARMS_rs10490924_T) demonstrated nonexudative neovascularization (38.1% vs. 22.1%), but this was not statistically significant ($P = 0.07$).

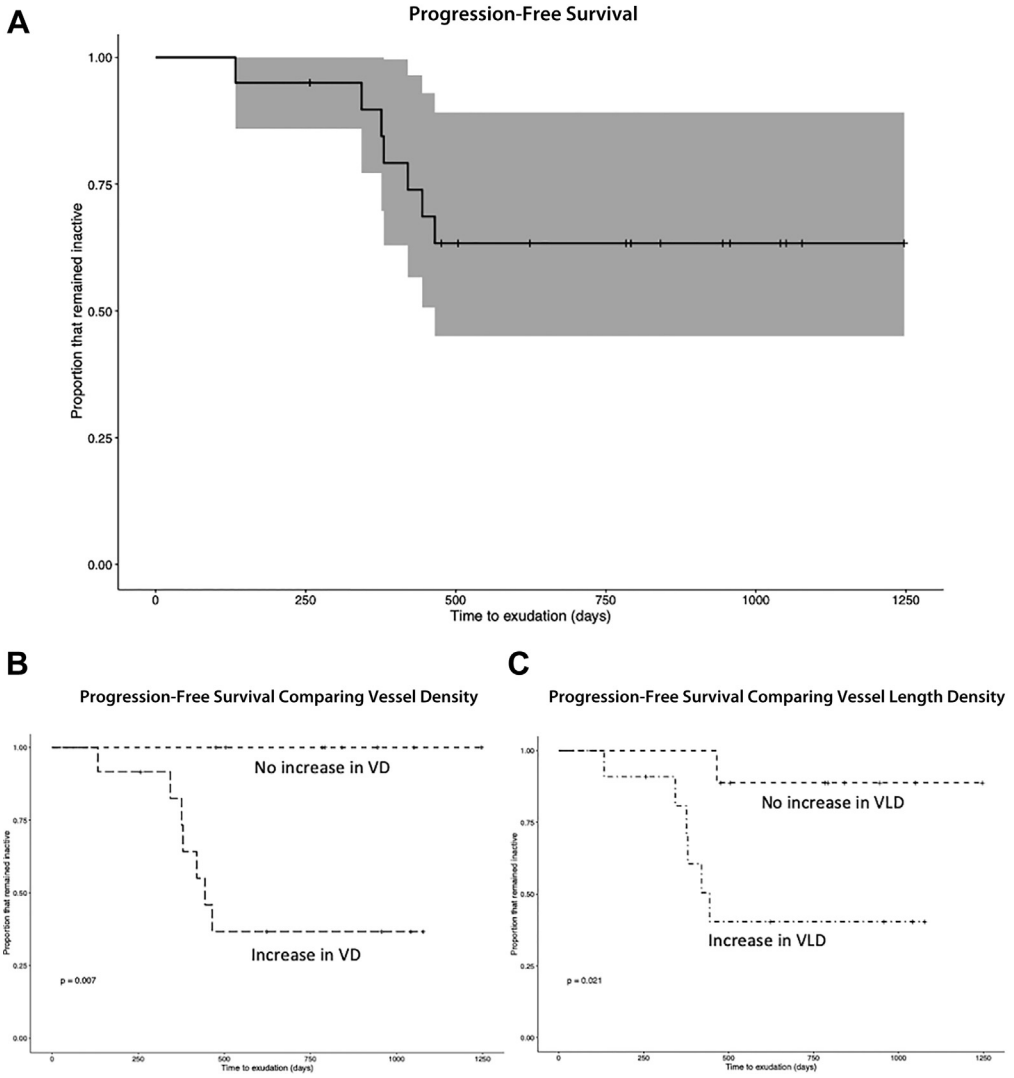

Figure 2. Kaplan-Meier plots showing progression-free events. **A**, Kaplan-Meier estimates of progression-free events in the overall population for eyes with OCT angiography-detected nonexudative neovascularization. **B**, **C**, Kaplan-Meier estimates of progression-free events according to significant quantitative measures of (**B**) vessel density (VD) and (**C**) vessel length density (VLD) increase. The cutoff for VD and VLD change to be considered significant was based on the interscan variation of 5.5% and 5.7%, respectively. A greater proportion of eyes remained inactive over time where there was no increase in VD and VLD.

Univariate and multivariate analyses are shown in Table 2. On univariate analysis, the odds of having nonexudative neovascularization was increased in smokers (OR, 2.65; 95% CI, 1.02−6.9; $P = 0.04$) and those with hyperlipidemia (OR, 2.32; 95% CI, 1.11−5.93; $P = 0.02$), higher cholesterol (OR, 1.55 per mmol/L; 95% CI, 1.1−2.36 per mmol/L; $P = 0.03$), higher triglycerides (OR, 1.91 per mmol/L; 95% CI, 1.21−3.83 per mmol/L; $P = 0.04$), and larger baseline GLD in the first presenting contralateral eye (OR, 1.33 per 500 μm; 95% CI, 0.4−1.71 per 500 μm; $P = 0.02$). Multivariate analysis after adjustment for significant risk factors showed that only hyperlipidemia (adjusted OR, 1.3; 95% CI, 1.10−3.20; $P = 0.04$), triglycerides (adjusted OR, 2.84 per mmol/L 95% CI, 1.06−4.35 per mmol/L; $P = 0.02$), and baseline GLD of the first presenting eye (adjusted OR, 1.6; 95% CI, 1.21−3.25 per 500 μm; $P = 0.03$) remained significant.

Comparison of Ocular Characteristics by Study Eye Status: Eyes without Nonexudative Neovascularization (n = 208) versus Those with Nonexudative Neovascularization (n = 21)

The baseline GLD of the choroidal neovascularization lesion measured on FA in the nonstudy eye was larger in persons whose study eye showed evidence of nonexudative neovascularization compared with those study eyes without such evidence (3763 ± 1252 μm vs. 4577 ± 1020 μm; $P = 0.02$). A numerical difference in baseline vision of the nonstudy eye between groups also was observed, but did not reach statistical significance (55.8 ± 13.2 letters vs. 47.3 ± 14.5 letters; $P = 0.06$). Also no significant differences were found in the lesion type in the non-study eye when analyzed by presence or absence of nonexudative neovascularization in the study eye.

Table 3. Baseline Characteristics of Eyes with Nonexudative Neovascularization That Progressed to Exudation versus Those That Did Not Progress

Characteristics	Nonprogressor (n = 13)	Progressor (n = 8)	*P* Value
Age (per yr), mean ± SD	68.2 ± 9.6	64 ± 4.2	0.89
Female gender, no. (%)	6 (46.2)	3 (37.5)	0.49
Ethnicity, no. (%)			
Chinese	10 (76.9)	5 (62.5)	0.97
Malay	1 (7.7)	2 (25)	
Indian	2 (15.4)	0 (0)	
Others	0 (0)	1 (12.5)	
BMI, no. (%)	(0)	(0)	
Underweight	2 (15.4)	0 (0)	0.67
Normal	10 (76.9)	6 (75)	
Overweight	1 (7.7)	2 (25)	
Obese	0 (0)	0 (0)	
Smoking	5 (38.5)	5 (62.5)	0.25
Diabetes	0 (0)	3 (37.5)	0.11
Hypertension	8 (61.5)	5 (62.5)	0.85
Hyperlipidemia	9 (69.2)	5 (62.5)	0.36
Angina	0 (0)	0 (0)	NA
Myocardial infarction	0 (0)	0 (0)	NA
Stroke	2 (15.4)	0 (0)	0.49
HbA1c (%), mean ± SD	5.5 ± 0.4	5.86 ± 0.3	0.27
Cholesterol (mmol/L), mean ± SD	5.9 ± 0.9	5.7 ± 0.7	0.98
HDL cholesterol (mmol/L), mean ± SD	1.72 ± 0.5	4.47 ± 0.1	0.46
Triglycerides (mmol/L), mean ± SD	2.165 ± 0.3	1.967 ± 0.3	0.36
LDL cholesterol (mmol/L), mean ± SD	3.794 ± 0.8	3.9 ± 0.4	0.92
Cholesterol-to-HDL ratio, mean ± SD	3.591 ± 0.4	5.867 ± 0.3	0.23
First eye features			
Baseline VA (letters), mean ± SD	47.2 ± 11.8	48.2 ± 11.4	0.78
Baseline GLD (μm), mean ± SD	4651 ± 1225	4428 ± 559	0.64
Lesion type, no. (%)	(0)		
PCV	4 (30.8)	3 (37.5)	0.65
Type 1 MNV	7 (53.8)	4 (50)	
Type 2 MNV	2 (15.4)	1 (12.5)	
Type 3 MNV	0 (0)	0 (0)	
Drusen type, no. (%)			
None	6 (46.2)	2 (25)	0.44
Pachydrusen	3 (23.1)	5 (62.5)	
Pseudodrusen	0 (0)	0 (0)	
Soft	4 (30.8)	0 (0)	
Soft + pachydrusen	0 (0)	1 (12.5)	
Soft + pseudodrusen	0 (0)	0 (0)	
Baseline VA (letters), mean ± SD	73.3 ± 6.6	67.7 ± 8.5	0.56
GLD (μm), mean ± SD	910 ± 461	1834 ± 552	<0.01
SFCT (μm), mean ± SD	262.2 ± 125.5	217 ± 78.3	0.47
Baseline lesion area (mm^2), mean ± SD	0.38 ± 0.59	0.62 ± 0.47	0.08
Baseline lesion vessel density (%), mean ± SD	55.3 ± 16.1	54.2 ± 18.4	0.95
Change in lesion size/year (%/year), mean ± SD	2.5 ± 2.3	4.8 ± 3.6	0.54
Change in VD/year (%/year), mean ± SD	1.1 ± 2.5	8.3 ± 4.1	<0.01
Change in VLD/year (%/year), mean ± SD	1.9 ± 3.6	15.6 ± 10.6	<0.01
CFH_rs800292_G (any risk allele present), no. (%)	9 (69.2)	6 (75.0)	0.92
ARMS_rs10490924_T (any risk allele present), no. (%)	10 (84.7)	12 (92.3)	0.44
CFH_rs800292_G and ARMS_rs10490924_T (all 4 risk alleles present), no. (%)	5 (38.5)	9 (42.9)	0.89

BMI = body mass index; CFH = complement factor H; GLD = greatest linear diameter; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MNV = macular neovascularization; PCV = polypoidal choroidal vasculopathy; SD = standard deviation; SFCT = subfoveal choroidal thickness; VA = visual acuity; VD = vessel density; VLD = vessel length density.

Table 4. Risk of Progression to Exudation

Characteristic	Progression			
	Odds Ratio (95% Confidence Interval)	P *Value*	*Adjusted Odds Ratio (95% Confidence Interval)**	P *Value*
Age (per yr)	0.92 (0.71–1.21)	0.56		
Female gender	1.67 (0.86–3.14)	0.49		
Ethnicity				
Chinese	Reference			
Malay	2 (0.13–9.14)	0.65		
Indian	0 (0–infinity)	0.99		
Others	0 (0–infinity)	0.99		
BMI				
Underweight	0 (0–infinity)	0.99		
Normal	Reference			
Overweight	2.52 (0.12, 6.21)	0.59		
Obese	0 (0–infinity)	0.99		
Smoking	3.21 (0.45–10.15)	0.26		
Diabetes	0 (0–infinity)	0.99		
Hypertension	0.83 (0.13–5.41)	0.85		
Hyperlipidemia	0.4 (0.06–2.89)	0.37		
Angina	0 (0–infinity)	0.99		
Myocardial infarction	0 (0–infinity)	0.99		
Stroke	0 (0–infinity)	0.99		
HbA1c (%)	1.95 (0.2–6.39)	0.23		
Cholesterol (mmol/L)	0.8 (0.13–4.89)	0.81		
HDL cholesterol (mmol/L)	0.2 (0–2.75)	0.41		
Triglycerides (mmol/L)	0.08 (0–2.13)	0.32		
LDL cholesterol (mmol/L)	1.01 (0.14–5.37)	0.99		
Cholesterol-to-HDL ratio	2.01 (0.44–9.28)	0.37		
First eye baseline VA (5 letters)	1 (0.91–1.21)	0.87		
First eye baseline GLD (per 500 μm)	1.1 (0.91–1.11)	0.86		
First eye lesion type				
PCV	Reference			
Type 1 MNV	0.3 (0.06–4.91)	0.57		
Type 2 MNV	0.3 (0.01–3.81)	0.98		
Type 3 MNV	0 (0–infinity)	0.99		
Nonexudative neovascularization (study) eye features				
Drusen				
None	Reference			
Present	0.38 (0.15–2.63)	0.65		
Pachydrusen	2.08 (0.38–5.48)	0.39		
Pseudodrusen	0 (0–infinity)	0.99		
Soft	0 (0–infinity)	0.99		
Soft + pachydrusen	0 (0–infinity)	0.99		
Soft + pseudodrusen	0 (0–infinity)	0.99		
Baseline GLD (μm per 500 μm)	1.3 (1.04–1.57)	0.02	1 (0.98–1.2)	0.32
SFCT (μm per 10 μm)	0.99 (0.97–1.1)	0.96		
Baseline lesion area (mm^2)	1 (0.98–1.20)	0.98		
Baseline lesion vessel density (%)	1.1 (0.97–1.21)	0.34		
Change in lesion size/yr (%/yr)	1.08 (0.93–1.25)	0.33		
Change in VD/yr (%/yr)	2.3 (1.63–7.65)	<0.01	1.7 (1.54–5.27)	0.01
Change in VLD/yr (%/yr)	1.8 (1.21–2.51)	<0.01	2.1 (1.71–3.12)	0.01
Genotype				
No risk alleles present	Reference			
CFH_rs800292_G (any risk allele present)	1.14 (0.08–16.95)	0.92		
ARMS_rs10490924_T (any risk allele present)	1.16 (0.09–17.42)	0.91		
CFH_rs800292_G and ARMS_rs10490924_T (all 4 risk alleles present)	1.20 (0.19–7.77)	0.84		

BMI = body mass index; CFH = complement factor H; GLD = greatest linear diameter; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MNV = macular neovascularization; PCV = polypoidal choroidal vasculopathy; SFCT = subfoveal choroidal thickness; VA = visual acuity; VD = vessel density; VLD = vessel length density.
*Adjusted for age, gender, baseline GLD, time from first visit of presenting eye in VLD, and change in VLD per year.

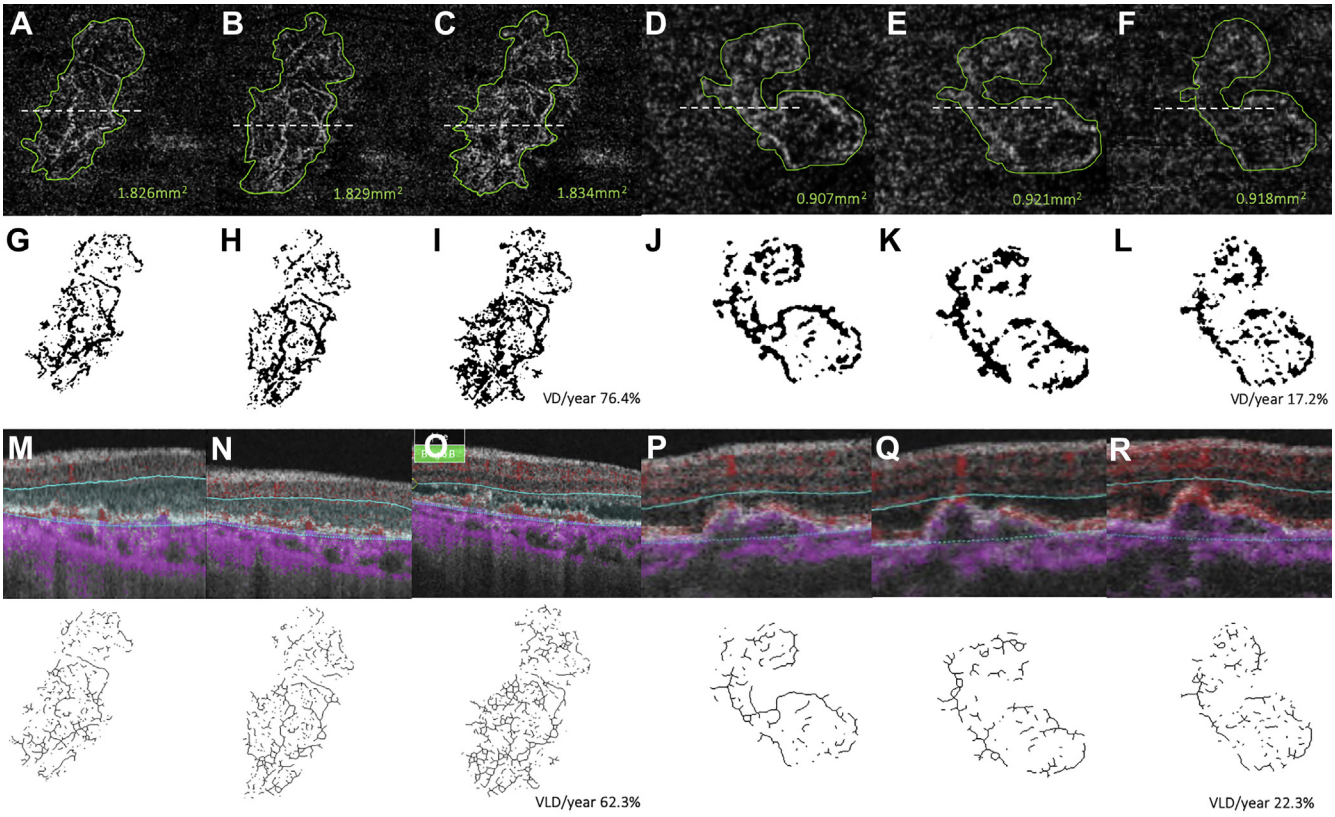

Figure 3. OCT angiography and OCT B-scan images of 2 eyes showing examples of progressor and nonprogressor eyes. **A**–**C**, Eye that progressed to exudation from the progressor group. The manually segmented lesions used for size measurement are denoted in green outlines. **G**–**I**, Vessel density (VD) segmentation (in black) and VD per year for each eye. **M**–**O**, Corresponding B-scans and slab used to obtain en face images (deep retina slab; Bruch's membrane to 70 μm below the inner plexiform inner nuclear layer border). **G**–**I**, Perceptible increase in VD as the eye progresses to exudation in 12 months, as seen on (**O**) OCT B scan, but lesion size remains similar. **D**, **E**, Eye in the nonprogressor group. **J**–**L**, Size and vessel density remain similar over time (3 years). **P**–**R**, OCT B scans showing minimal changes.

Clinical Features by Study Eye Progressor Status (Progressor Group, n = 8) versus Those That Did Not Progress to Exudative Neovascular Age-Related Macular Degeneration (Nonprogressor Group, n = 13)

Of the 21 study eyes with nonexudative neovascularization at baseline, duration of follow-up was 839 ± 145 days and progression to exudation occurred in 8 eyes (3 of these demonstrated a polyploidal choroidal vasculopathy [PCV] variant in the presenting eye). Mean visual acuity did not change significantly from baseline, nor were differences between progressor and nonprogressor groups found. The mean time to progression in study eyes with nonexudative neovascularization was 377 ± 88 days in the progressor group, as shown in the Kaplan-Meier curve (Fig 2A) Patient and ocular characteristics comparing nonprogressors and progressors are summarized in Table 3.

Comparison between Nonprogressors and Progressors

No significant difference was found in age (68.2 years vs. 64.0 years; $P = 0.89$), gender (female, 46.2% vs. 37.5%; $P = 0.49$), ethnicity ($P = 0.97$), blood chemistry, or CFH_rs800292_G and *ARMS2* genotype. The baseline GLD measured on OCTA of the nonexudative neovascularization lesion in the study eye was significantly smaller in the nonprogressor group compared with the progressor group (910 ± 461 μm vs. 1834 ± 552 μm, respectively; $P < 0.01$). The baseline area was lower in the nonprogressor group compared with the progressor group (0.38 ± 0.59 mm^2 vs. 0.62 ± 0.47 mm^2, respectively; $P = 0.08$), although this did not reach statistical significance. With respect to other baseline characteristics, no difference was found in visual acuity ($P = 0.77$), type of drusen ($P = 0.24$), lesion type ($P = 0.65$), mean subfoveal choroidal thickness ($P = 0.47$), mean VD ± standard deviation ($P = 0.95$), and VLD ($P = 0.95$).

OCT Angiography Changes in Nonexudative Neovascularization

On comparing progressors with nonprogressors (Table 4), a larger rate of increase in mean VD per year ($P = 0.01$) and mean VLD per year ($P = 0.01$) was observed. The change in lesion area was not significant between the 2 groups (progressor, 37.5% vs. nonprogressor, 15.4%; $P = 0.11$). A higher proportion of eyes in the progressor group showed a demonstrable increase in the VD per year and the VLD per year that was greater than the interscan variation for each measure compared with the

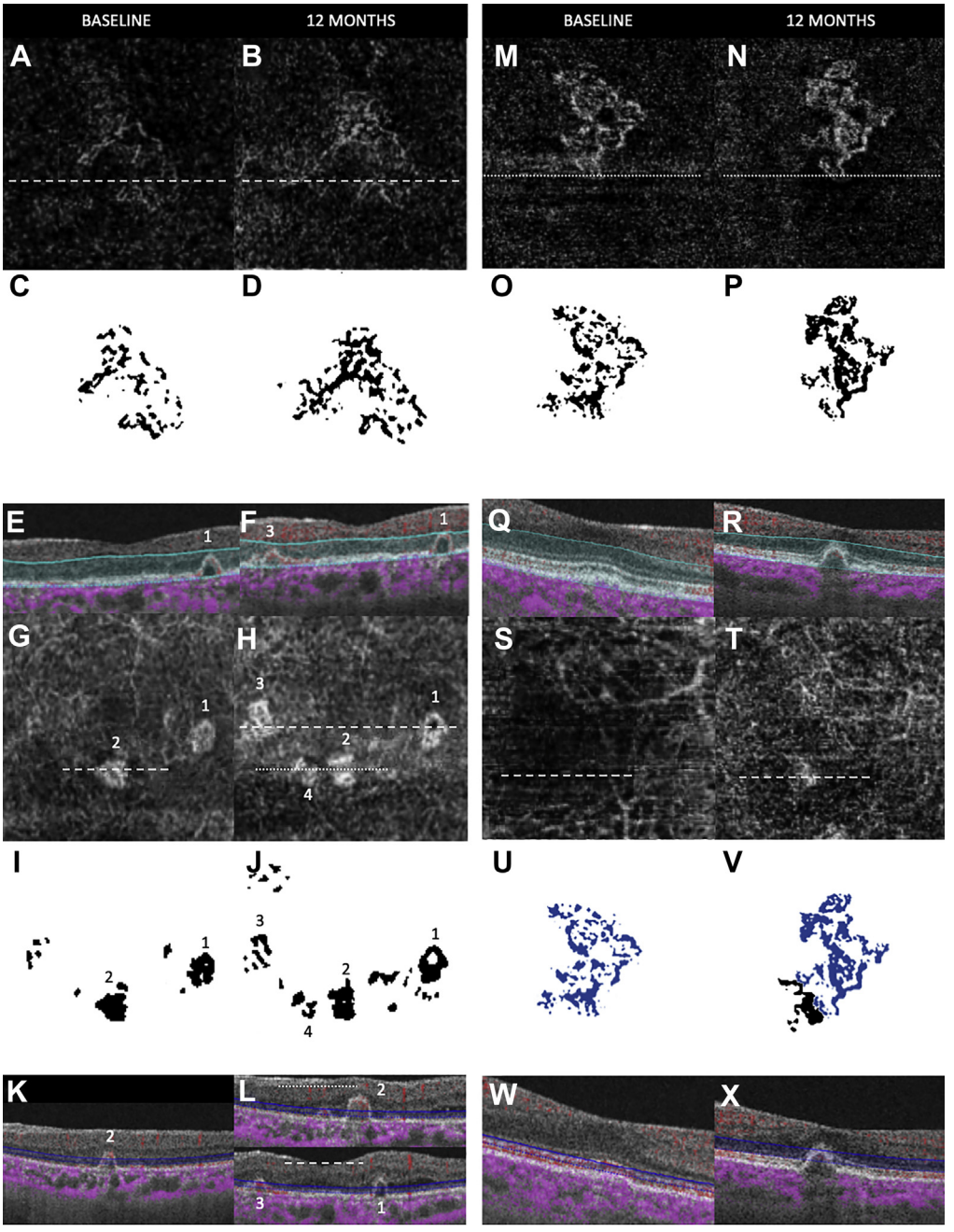

Figure 4. Images showing the progression of an eye in the progressor group with aneurysmal lesions from baseline and progressive increase in the number of aneurysmal lesions over time. Left column (**A**–**L**) shows 1 eye that progressed to exudation after 12 months. **A**, **B**, En face OCT angiography (OCTA) image with (**E**, **F**) corresponding B-scan (outer retina slab in the blue outline: Bruch's membrane [BM] to 70 μm below the inner plexiform inner nuclear layer border) and the (**C**, **D**) ImageJ-processed image of the lesion. The B-scan showed the detection of new pigment epithelial detachment (PED) lesion at 12 months, labelled 3 on (**F**) B-scan and (**H**) en face image. When the segmentation was adjusted manually (slab of 50 μm following the BM line placed at the level of the PED), the aneurysmal lesions are much better detected on corresponding en face OCTA: aneurysmal lesions numbered 1–4 and on corresponding B-scans (**H**). **I**, **J**, ImageJ processing technique reveals the increase in aneurysmal lesions from baseline. Exudation eventually occurred in this eye (B-scan with the long dash, inset panel [**L**]), first detected from an old aneurysmal lesion (1 and 2) that had been present since baseline (**G**, **H**, **K**, **L**). Right column (**M**–**X**) shows OCTA images of an eye that had no aneurysmal lesions detected at baseline, but demonstrated new aneurysmal lesions over time. En face OCTA scan of (**M**, **N**) the outer retina slab with (**O**, **P**) ImageJ processed image of the lesion and (**Q**, **R**) corresponding B-scans. Note (**Q**) the absence of PED at baseline and (**R**) the detection of new PED at follow-up. Manually adjusted slab (50 μm following the BM line placed at the level of the PED [**W**, **X**]) reveals better detection of new aneurysmal lesion at 12 months on (**S**, **T**) en face scan and (**V**) corresponding ImageJ image at the inferior tip of the neovascular network, which was not present at baseline. The vascular lesion imaged at the outer retinal slab (blue) is superimposed on (**U**, **V**) to orientate the position of the new aneurysmal lesion (black) in relation to the lesion detected with the outer retina slab.

nonprogressor group (VD, 87.5% vs. 38.5% [$P = 0.01$] and VLD, 75.0% vs. 38.5% [$P = 0.04$], respectively). OCT angiography features of progressor and nonprogressor eyes are shown in Figure 3.

Within the progressor group only, the mean number of days ± standard deviation from the baseline visit to the first visit with a demonstrable increase in VD and VLD without signs of exudation was 219 ± 68 days. The interval between the visit where the increase in VD and VLD was documented to the occurrence of exudation was 157 ± 55 days. Time to progression in the eyes comparing increase in VD and VLD is shown in the Kaplan-Meier curve (Fig 2B, C).

Aneurysmal Lesions in Nonexudative Neovascularization

In eyes with nonexudative neovascularization and pachychoroid features that progressed to exudation (n = 3), new aneurysmal lesions seemed to develop at the terminal ends of neovascular network along with an increase in VD and VLD. The diagnosis in the first presenting eye was PCV in all 3 cases. Exudation occurred adjacent to the aneurysmal terminal ends of the neovascular network (Fig 4). No significant difference was found between mean ± standard deviation time to exudation in eyes with PCV (n = 3) versus eyes without PCV (n = 5; 417 ± 148 days vs. 354 ± 117 days; $P = 0.90$).

Discussion

This study reports several novel findings with respect to the natural history and the progression pattern of nonexudative neovascularization lesions in the fellow eyes of patients demonstrating unilateral exudative nAMD. First, we observed a significant increase in the risk of nonexudative neovascularization in persons with hyperlipidemia. Second, patients with larger lesions in the presenting eye showed an increased risk of nonexudative neovascularization in the second eye. Third, a larger nonexudative neovascularization lesion at baseline and a faster rate of increase in VD within the lesion over time were predictors of faster progression to exudative nAMD. Finally, this study examined the temporal characteristics of eyes with nonexudative nAMD, thus providing data of prognostic importance and frequency of monitoring.

Prior studies on nonexudative neovascularization have reported that between 6% and 18% of fellow eyes of patients with unilateral nAMD are likely to exhibit nonexudative neovascularization.[4,12,14,15,36,37] In our case series, which is one of the largest to date, we observed that 9% of patients demonstrated nonexudative neovascularization in the fellow eye, which is in agreement with the range reported. Prior studies generally have been small, including an earlier report from our own group in which we observed a prevalence of 18% of eyes with nonexudative neovascularization in a sample of 76 patients. If we restricted our observations to cohorts of more than 100 patients, the prevalence of nonexudative neovascularization reduced to 13% to 14%, which is more similar to that observed in the present study. Another possible reason for the lower prevalence that we observed is the predominantly Asian ethnicity of the sample in the current study, in whom progression in the fellow eye may be different to that of White persons. Finally, our patients were younger, with the age ranging from 50 to 70 years, compared with the range of 50 to 90 years that is common in studies in Western White populations.

Our study is the first to report an association between nonexudative neovascularization and systemic risk. Another novel finding in our study is the lower visual acuity in the first presenting eye in those who demonstrated nonexudative neovascularization when compared with those who did not exhibit this finding in the study eye, suggesting more severe disease in the first eye. The GLD in the first presenting eye also was greater when nonexudative neovascularization was detected in the fellow eye. It is unclear whether this finding has arisen because of later presentation of the first involved eye or whether the bilateral findings signify a more severe disease phenotype. Some of our results support the latter hypothesis. First, we found that hyperlipidemia, particularly serum triglycerides, confer a greater risk for the presence of nonexudative neovascularization in the fellow eye. Dyslipidemia consistently has been described as a risk factor for nAMD.[38–40] Our findings, which show a linkage between bilateral pathologic features at initial presentation with dyslipidemia, further support the hypothesis that lipid dysregulation is involved in the pathogenesis of nAMD and also likely exacerbates the severity of disease. We acknowledge that these results are subject to self-reporting bias because the diagnosis of hyperlipidemia was self-reported in this cohort. This is partially mitigated because lipid analytics were available. Statin use may have had a normalizing effect on lipid levels, and we acknowledge this as a limitation and as a potential confounder that may have affected the findings. Second, we found a trend to significance that homozygosity of risk alleles of both CFH_rs800292_G and ARMS_rs10490924_T was associated with nonexudative neovascularization. These results are consistent with previous studies that showed increased genetic risk with more severe forms of AMD such as progression from early to nAMD,[41] poorer visual acuity, bilaterality,[42] and poorer response to treatment.[43] A larger cohort may provide more clarity on the effects of genetic load on nonexudative neovascularization.

If we considered nonexudative neovascularization as an early form of bilateral involvement, we would expect the association of nonexudative neovascularization to follow the pattern of bilaterality noted in the different lesion subtypes. For instance, retinal angiomatous proliferation lesions, or type 3 macular neovascularization (MNV), were found to have the highest rate of bilateral involvement compared with types 1 and 2 MNV.[17,44] However, this correlation was not shown in this study and likely because of the relatively low prevalence rate of type 3 MNV in the Asian population and that not enough patients with type 3 MNV were observed for sufficient power.[45]

Other results from this study also address existing knowledge gaps regarding the progression of nonexudative neovascularization to exudation. Some suggest that these nonexudative neovascularization lesions protect the damaged and ischemic retina from progression to atrophy,[46]

whereas others suggest that these lesions herald the development of exudative nAMD.[9–13] Currently, data are lacking regarding the risk associated with nonexudative neovascularization. In our study, an annual estimated incidence of 19% progression was observed, with most conversions to exudative nAMD occurring within the first 1.5 years from initial presentation of the first eye. This finding is consistent with a previous report from our group[13] and also with a previous study on the natural history of subclinical neovascularization that reported an incidence of 21%.[37] It is notable that most eyes with nonexudative neovascularization remained quiescent with no perceivable decline in vision during the period of follow-up. These data show that vision is lost from the consequences of the exudative neovascularization lesion, with fluid accumulating in retinal compartments, followed by secondary fibrosis or atrophy, rather than the neovascularization network itself, which, in the absence of any process disrupting anatomic features, may serve as a compensatory mechanism protective against end-stage consequences like macular atrophy.[46–50]

Currently, the management of nonexudative neovascularization remains controversial. Most clinicians will opt not to treat these lesions until signs of exudation or hemorrhage ensue, but it is widely accepted that closer monitoring is desirable because these eyes are at 7 to 15 times higher risk of exudation developing compared with eyes without these subclinical OCTA lesions.[13,36,51] However, the optimal monitoring interval also is understood poorly, and it is unclear how to predict which of these nonexudative lesions are at a higher risk of activation and progression to exudation. To help clinicians identify eyes at higher risk of exudation developing, we found that a larger baseline lesion, an increase in VD per year and in VLD per year, and a qualitative increase in vascular network density of the nonexudative neovascularization during follow-up are important predictors of exudation and new activity. This finding is in keeping with a recent study that used custom software to quantify VD automatically and reported a similar association with exudation in eyes with nonexudative neovascularization.[51]

Although most patients with exudative nAMD in the contralateral eye are likely to be undergoing follow-up, frequently allowing the eye without exudation to be monitored, a deeper scrutiny is less likely to be needed until changes in the VD and VLD appear. The mean interval to detection of a significant and observable change in VD and VLD of vasculature in the current series was 219 ± 98 days, and a further 157 ± 75-day gap was noted before progression to exudation. This interval offers an important window of opportunity to escalate the level of surveillance in clinical monitoring. No difference was found between precursor imaging biomarkers for typical nAMD and PCV, suggesting that the increase in VD and VLD of the lesion is applicable over both subtypes of AMD.

The origin of aneurysmal lesions has remained a topic of controversy. It is increasingly accepted that the vascular network within a PCV complex is similar to a type 1 neovascular network. Some authors have proposed that aneurysmal lesions may develop in eyes with chronic type 1 neovascularization, especially if accompanied by a pachychoroid background.[52–55] This theory was supported by our findings in which new aneurysmal lesions developed in 3 eyes with a nonexudative neovascularization with pachychoroid background. Interestingly, although an increase in VD and VLD across the entire lesion was noted, exudation developed around the new aneurysmal lesions. However, in view of the heterogeneity of PCV lesions, more eyes will need to be evaluated to understand fully the interaction between the polypoidal lesion and the vascular network.

Strengths of the current study include the relatively long follow-up, detailed assessment of systemic risk, and inclusion of patients with PCV, with assessment of images using objective quantifiable parameters. In addition, we evaluated interscan variability to ensure that longitudinal changes in OCTA quantitative measures were clinically meaningful and constituted significant changes. Our study has a number of limitations. Although it is one of the largest of its kind, only 21 patients demonstrated nonexudative neovascularization at presentation, and we may not have had sufficient power to detect other risk factors that may be associated with the presence of nonexudative neovascularization or progression to exudation. In addition, past medical history and use of medications were self-reported and may have been prone to self-reporting bias. However, we believe that our use of blood levels of lipid and cholesterol is a mitigating factor. Also, currently a lack of validated quantification methods for OCTA exist owing to the susceptibility of this technology to segmentation and projection artefacts, which becomes even more problematic when trying to compare segments longitudinally.[56–58] Quantitative measures obtained on VD and lesion area required adjustments of the outer retinal slab boundaries before export into ImageJ. This method, while ensuring that the lesion segmentation is robust, is difficult to apply in routine clinical settings and also may not be reproducible. However, because eyes with nonexudative lesions do not exhibit severe distortion of retina anatomic features, fewer artefacts exist that can affect accurate segmentation. Furthermore, to mitigate the effects of artefacts, we standardized our methods for quantification and we applied them consistently across all scans at all time points.

Conclusions

We identified differences in baseline characteristics between patients with and without nonexudative neovascularization in the fellow eye. More than one third of fellow eyes with nonexudative neovascularization at baseline progressed to exudation, suggesting that close monitoring of these patients is recommended, particularly after the first 18 months. Larger baseline lesion size is the only predictive baseline factor identified. However, an increase in VD and VLD during follow-up on OCTA was predictive of subsequent progression to exudation. Hence clinically, as soon as any of these changes is observed, the follow-up interval should be shortened for closer monitoring and possible treatment.

Footnotes and Disclosures

Originally received: April 9, 2020.
Final revision: June 18, 2020.
Accepted: July 8, 2020.
Available online: July 14, 2020. Manuscript no.ORET-2020-252.

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Disclosure(s):
All authors have completed and submitted the ICMJE disclosures form.
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Supported by the National Medical Research Council, Singapore, Republic of Singapore (Large Collaborative Grant [G.C.M.G.]) Grant number NMRC/OFLCG/004/2018.

HUMAN SUBJECTS: Human subjects were included in this study. The human ethics committees at Singhealth approved the study. All research adhered to the tenets of the Declaration of Helsinki. Written consent was provided by all patients in this study.

No animal subjects were included in this study.

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Analysis and interpretation: Teo, Cheung

Data collection: Teo, Yanagi, Cheung

Obtained funding: National Medical Research Council

Overall responsibility: Teo, Yanagi, Wong, Charkaravarty, Cheung

Abbreviations and Acronyms:
CFP = color fundus photography; **CI** = confidence interval; **FA** = fluorescein angiography; **GLD** = greatest linear diameter; **MNV** = macular neovascularization; **nAMD** = neovascular age-related macular degeneration; **OCTA** = OCT angiography; **OR** = odds ratio; **PCV** = polyploidal choroidal vasculopathy; **VD** = vessel density; **VLD** = vessel length density.

Keywords:
Age-related macular degeneration, Anti−vascular endothelial growth factor, Nonexudative neovascularization, OCT angiography, Retina.

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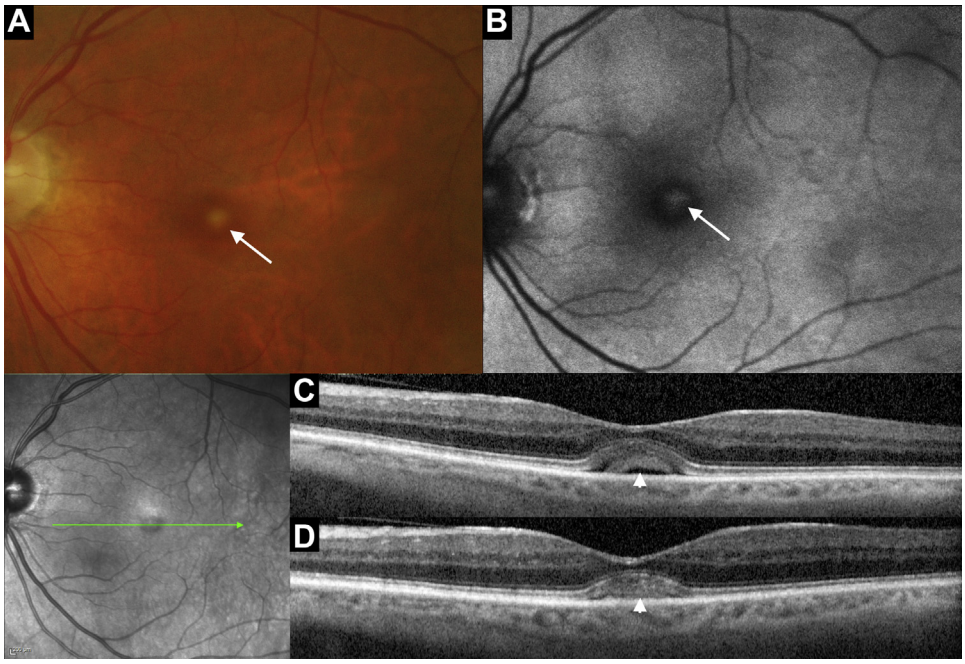
Pictures & Perspectives



Pseudovitelliform Maculopathy Associated with FGFR Inhibitor Therapy

An 84-year-old man presented with bilateral visual disturbances 1 week after starting erdafitinib, a fibroblast growth factor receptor (FGFR) inhibitor, for metastatic urothelial carcinoma. Tumor genomic profiling revealed FGFR1 amplification and FGFR3 mutations allowing off-label use of erdafitinib (8 mg/day). Ophthalmoscopy showed foveal yellowish deposit (**A**, arrow) that appeared hyperautofluorescent on fundus autofluorescence (**B**, arrow). OCT revealed subretinal fluid with hyperreflective material adherent to diffusely thickened ellipsoid/interdigitation zones (**C**, arrowhead). Spontaneous regression of subretinal fluid was observed despite drug continuation (**D**, arrowhead). Acquired vitelliform lesions may expand the spectrum of ocular adverse events associated with FGFR inhibitors.

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