Prevalence and Risk Factors for Nonexudative Neovascularization in Fellow Eyes of Patients With Unilateral Age-Related Macular Degeneration and Polypoidal Choroidal Vasculopathy

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Purposes. To determine the prevalence of subclinical nonexudative neovascularization and associated choroidal vascular changes in the fellow eyes of patients presenting with unilateral typical exudative AMD (tAMD) or polypoidal choroidal vasculopathy (PCV) using indocyanine green angiography (ICGA) and swept-source (SS) optical coherence tomography angiography (OCT-A).

Methods. We recruited patients presenting with tAMD or PCV in a prospective clinical study. The diagnosis in the presenting eye was determined based on clinical, fluorescein angiography (FA), and ICGA findings. We evaluated the contralateral eye for presence of nonexudative neovascularization, choroidal hyperpermeability, and pachyvessels in the outer choroid, based on multimodal imaging which included ICGA, spectral-domain (SD) OCT and OCT-A. We measured subfoveal choroidal thickness in both eyes for each patient.

Results. We included 76 fellow eyes of 76 patients who presented with unilateral tAMD (n = 43) or PCV (n = 43). Nonexudative neovascularization was present in 18% eyes (14 eyes, 8 in tAMD group, 6 in PCV group; 7 on ICGA, 4 on OCT-A, 3 on both ICGA and OCT-A). Pachychoroid pigment epitheliopathy was present in 15 eyes with nonexudative neovascularization, and was the only risk factor associated with nonexudative neovascularization.

Conclusions. Approximately one in five fellow eyes with unilateral tAMD and PCV have features of nonexudative neovascularization. The use of multimodal imaging including ICGA and OCT-A can identify these features. The presence of pachychoroid epitheliopathy should alert clinicians to the possibility of underlying neovascularization.

Keywords: age-related macular degeneration, nonexudative neovascularization, optical coherence tomography angiography

Age-related macular degeneration is a major global public health concern, and projected to affect nearly 300 million people by 2040.1 Age-related macular degeneration is classified as early and intermediate AMD, with features of drusen and retinal pigment epithelial (RPE) changes, and late AMD, which includes exudative AMD, characterized by the presence of choroidal neovascularization (CNV).2 Clinical fundus examination showing the presence of exudation and hemorrhage is the sine qua non of CNV. More recently, however, histologic studies have demonstrated the presence of “nonexudative neovascularization” in some eyes with early or intermediate AMD.3,4 Moreover, clinical studies have been able to detect nonexudative neovascularization as a hyperfluorescent plaque using indocyanine green angiography (ICGA),5,6 or as blood flow signal under the RPE using optical coherence tomography angiography (OCT-A).5–10 The exact frequency of such “nonexudative neovascularization” is unclear, but prevalence between 11% and 27% has been reported in previous studies in white patients.6,9,10

It is clinically important to understand the frequency of nonexudative neovascularization in the contralateral eyes of unilateral exudative AMD because a quarter of such eyes may develop exudative AMD over 4 years.11,12 There have been limited studies regarding the frequency of bilateral disease in Asian populations.13,14 In particular, the prevalence of bilateral disease in polypoidal choroidal vasculopathy (PCV) has been suggested to be lower than in typical exudative AMD (tAMD). Moreover, it has recently become clear that various characteristic choroidal vasculature features are associated with exudative maculopathy using multimodal imaging.7,15–20 Freund and colleagues15–17 have proposed the term “pachychoroid spectrum” to include dilated pachyvessels, choroidal vascular hyperpermeability (CVH), pachychoroid pigment epitheliopathy,18 and pachychoroid neovascularopathy.19 These features may reflect chronic changes within the choroidal vasculature that predispose to neovascularization. We hypothesize that choroidal vascular abnormalities may predict the presence of nonexudative neovascularization in Asian patients. In the current study, we...
investigated the prevalence of nonexudative neovascularization in contralateral eyes in patients with unilateral tAMD or PCV. We also determined the choroidal vasculature features in these asymptomatic contralateral eyes on multiple imaging modalities.

**METHODS**

**Subjects**

Data for this study was taken from a prospective, observational cohort study involving patients with exudative AMD in the Asian AMD Phenotyping Study. Detailed methodology has been published elsewhere. The study was approved by the Singhealth Centralized institutional review board and was conducted according to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each patient before participation in the study. The data for this study was taken from patients recruited between October 2015 and March 2016 at the Singapore National Eye Centre.

**Clinical Examinations**

All patients had a standardized history, clinical examination including measurement of best-corrected visual acuity, slit-lamp biomicroscopy indirect fundus examination, and underwent fluorescein angiography (FA) and ICGA performed with the Heidelberg Spectralis HRA (Heidelberg Engineering, Heidelberg, Germany) or flash camera (TRC-50DX, Topcon, Tokyo, Japan). Swept-source (SS) OCT-A (DRI OCT Triton; Topcon), together with SD-OCT with enhanced-depth imaging (EDI) mode (Spectralis; Heidelberg Engineering). Thirty degrees of retina were scanned along the horizontal planes through the foveal center. The averaging systems of OCT were used and 30 images were averaged for each scan.

**Diagnosis of tAMD and PCV**

Exudative AMD was diagnosed when there was evidence of CNV associated with nondrusenoid RPE detachment, serous or hemorrhagic retinal detachment, subretinal hemorrhage, or subretinal exudation. According to FA, ICGA, and OCT findings, patients with exudative AMD were divided into two subgroups consisting of those with typical CNV and those with PCV. Polypoidal choroidal vasculopathy was diagnosed based on the criteria of the Japanese Ophthalmological Society, which define PCV as the presence of a polypoidal lesion with a branching vascular network on ICGA, with concomitant exudation or hemorrhage.

**SS-OCT-A Image Acquisition**

Swept-source OCT-A enface images (SS OCT Angio; Topcon) were used to evaluate presence of flow signals. The SS-OCT-A is based on Topcon OCT Angiography Ratio Analysis algorithm (OCTARA). The instrument uses a light source with a center wavelength of 1050 nm, and scans at speed of 100,000 A-scans per second, which yields axial resolution of 8 μm and depth of 2.4 dB/mm. Each OCTA volume scan contains 320 × 320 pixels and covers an area 3 × 3 mm. OCTARA is based on detecting the degree of motion between consecutive OCT images. Briefly, OCT B-scan images are collected at the same transverse location four times. These four images are registered with each other using registration algorithm. The degree of motion is then calculated to allow extraction of blood flow. The above procedure is then repeated for a different Vposition in the retina to achieve the three-dimensional dataset and to reconstruct en face OCT-A images.

**Image Grading**

Each eye was imaged with color fundus photography, FA, ICGA, SD-OCT, and SS-OCTA during the same visit. A qualitative analysis and comparisons of the entire imaging data set were conducted. Color fundus photos were used to grade for the presence of large drusen (soft distinct or soft indistinct drusen with diameter ≥125 μm). Indocyanine green angiography images were used to evaluate presence of vascular network vessels (nonexudative neovascularization), CVH, and presence of pachyvessels. On ICGA, the eyes were diagnosed with CNV when they exhibited focal choroidal hyperfluorescence (plaque) in late frame of ICGA with or without clear evidence of neovascular networks (Figs. 1–3). Choroidal vascular hyperpermeability was characterized by multifocal choroidal hyperfluorescence with blurred margins, and dilated and hyperpermeable choroidal blood vessels, or pachyvessels. Pachyvessels were best visualized in the early to mid phase ICGA images. Cross-sectional SD-OCT was used to measure central choroidal thickness and was also used to evaluate the presence of drusen, reticular pseudodrusen (RPD), and pachyvessels. Subfoveal choroidal thickness (CT) was measured using the built-in measuring tool of the SD-OCT. Pachyvessels in the current study were defined as dilation of luminal area with/without a concomitant thinning of the overlying choriocapillaris layer. En face SS-OCTA was used to access the presence of flow signals or neovascular tissue in the plane above Bruch’s membrane. Automated segmentation was used for the analysis and when automated segmentation failed to show flow signals, the area of segmentation was manually adjusted until the tissue of interest was visualized. On OCT-A, the eyes were diagnosed with CNV when the scans of the outer retinal layer, where flow signals are normally absent, showed a vascular network (Figs. 1–3). In cases where outer retinal slabs showed faint flow signal of neovascularization, choroidal slab was also used as a reference. On choriocapillaris slab, OCT-A images were inspected especially focusing on aberrant flow. Swept-source OCTA volumes of the outer choroid were inspected for the presence of pachyvessels. Characteristic features of pachyvessels included dilated outer choroidal vessels, which retain a large caliber as they traverse the macula and/or club-shaped posterior terminal morphology of the choroidal vessels. Pachychoroidal pigment epitheliopathy was diagnosed based on the report by Freund and colleagues. All images were evaluated by three retinal specialists (YY, AM, and GC) independent of conventional angiography and masked to fellow eye diagnosis of tAMD and PCV. In case of discordance, the results were adjudicated by a senior retinal specialist (GC).

Statistical analysis was carried out using JMP software version 11.0 (SAS Institute, Cary, NC, USA). Univariate analysis was performed using Student’s t-test for numerical data and Fisher's exact probability test for categorical data; any P value not exceeding 0.05 was regarded as statistically significant. To find independently associated factors for nonexudative neovascularization, multivariate analysis was performed on factors with significance (P < 0.05) in univariate analysis.

**Results**

We included 76 eyes of 76 patients with unilateral exudative AMD, after excluding 23 subjects who had macular scar in the contralateral eye, or poor quality OCT-A scans due to eye movement (motion artifact) or media opacity. Of the 76 patients, 35 had tAMD and 43 had PCV. The mean age was similar between patients with tAMD and PCV (71.0 vs. 69.6 years, P = 0.471). The majority of patients were male (72% in the tAMD group and 51% in the PCV group, P = 0.064),
We identified 14 eyes (18%) with nonexudative neovascularization (8 in the tAMD group and 6 in the PCV group, $P = 0.371$). Nonexudative neovascularization was detected on both ICGA and OCT-A in three eyes (Fig. 1), on ICGA alone in seven eyes (Fig. 2), and on OCT-A alone in four eyes (Fig. 3). The Cohen’s Kappa values for intergrader reliability was calculated between two senior graders (GC and YY) of the three graders, to assess the agreement between graders. The Kappa values were calculated separately for each imaging modality (ICGA and OCT-A) and for the combined modality (ICGA + OCT-A). The Kappa values were found to be satisfactory, indicating a good intergrader agreement.

**Nonexudative Neovascularization and Related AMD Features**

We identified 14 eyes (18%) with nonexudative neovascularization (8 in the tAMD group and 6 in the PCV group, $P = 0.371$). Nonexudative neovascularization was detected on both ICGA and OCT-A in three eyes (Fig. 1), on ICGA alone in seven eyes (Fig. 2), and on OCT-A alone in four eyes (Fig. 3). The Cohen’s Kappa values for intergrader reliability was calculated between two senior graders (GC and YY) of the three graders, to assess the agreement between graders. The Kappa values were calculated separately for each imaging modality (ICGA and OCT-A) and for the combined modality (ICGA + OCT-A). The Kappa values were found to be satisfactory, indicating a good intergrader agreement.

**Figure 1.** Nonexudative neovascularization visualized with both ICGA and OCT-A. Optical coherence tomography angiography shows flow signals from nonexudative neovascularization using the outer retinal slab (*top panels*). Cross-sectional OCT scan through the foveal center of the left (case 1) right (cases 2 and 3) eye shows undulation of the RPE line. Nonexudative neovascularization is also visualized by ICGA (*bottom panels*). Neovascularization is evidenced by the presence of abnormal branching vascular network in the early frame of ICGA.

**Figure 2.** Nonexudative neovascularization visualized with ICGA but not with OCT-A. (A) Fundus photograph show pigmentary lesion superior and temporal to the foveal center of the right eye (*arrows*). (B) Nonexudative neovascularization visualized by ICGA. Neovascularization is evidenced by focal area of hyperfluorescence in the late frame of ICGA. (C) Cross-sectional OCT scan through the foveal center of the right eye shows undulation of the RPE line and concomitant thickening of the choroid. The innermost layer of the choroid is attenuated. (D) Optical coherence tomography angiography. En face OCT-A images using outer retinal slab (*upper panel*), choroidal slab (*middle panel*), and composite color-coded image (*lower panel*) are shown. Optical coherence tomography angiography failed to provide clear visualization of the neovascularization in the outer retinal slab. *Middle panel* shows pachyvessels in the outer choroid.

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**Figure 2.** Nonexudative neovascularization visualized with ICGA but not with OCT-A. (A) Fundus photograph show pigmentary lesion superior and temporal to the foveal center of the right eye (*arrows*). (B) Nonexudative neovascularization visualized by ICGA. Neovascularization is evidenced by focal area of hyperfluorescence in the late frame of ICGA. (C) Cross-sectional OCT scan through the foveal center of the right eye shows undulation of the RPE line and concomitant thickening of the choroid. The innermost layer of the choroid is attenuated. (D) Optical coherence tomography angiography. En face OCT-A images using outer retinal slab (*upper panel*), choroidal slab (*middle panel*), and composite color-coded image (*lower panel*) are shown. Optical coherence tomography angiography failed to provide clear visualization of the neovascularization in the outer retinal slab. *Middle panel* shows pachyvessels in the outer choroid.
which showed overall good agreement (0.737 for OCT-A and 0.554 for ICGA). The results suggest an OCT-A sensitivity of 50% as compared with 71% sensitivity of ICGA for detection of nonexudative neovascularization.

The prevalence of other ocular features including drusen, RPD, CVH, and pachychoroid pigment epitheliopathy, stratified by diagnosis of tAMD versus PCV is also summarized in Table 1. Although there were numerical differences in the proportion of eyes with RPD (tAMD group 27%, PCV group 9.3%) and CVH (tAMD group 52%, PCV group 32%), none of these differences reached statistical significance. Mean CT was 226 \text{ lm} in the tAMD group and 223 \text{ lm} in the PCV group (\( P = 0.876 \)). Although eyes with RPD had thinner choroid (179 vs. 233 \text{ lm}, \( P = 0.042 \)) and higher frequency of drusen (92% vs. 51%, \( P = 0.006 \)) than eyes without RPD, there was no difference in other choroidal vasculature features in the tAMD group and PCV group stratified by the presence/absence of RPD.

The ocular risk factors for presence of nonexudative neovascularization were evaluated in Table 2. Pachychoroid pigment epitheliopathy was observed in 93% of eyes with nonexudative neovascularization compared with 37% in those without neovascularization (\( P < 0.001 \)). Detection of pachyvessels (on ICGA and on all 3 modes) was associated with nonexudative neovascularization in a univariate analysis; however, none of the ocular factors studied except pachychoroid pigment epitheliopathy were significantly different between eyes with and without nonexudative neovascularization.

We also performed layer-by-layer analysis of OCTA in the 14 eyes with nonexudative neovascularization. Pachyvessels in the Haller’s layer were identified beneath the area of neovascularization in 85% (12 eyes). In addition, choriocapillaris layer disturbance in the area of pachyvessels were noted in 50% (7 eyes; Fig. 4).

**Discussion**

In the current study, combination of ICGA and OCT-A identified nonexudative neovascularization in 18% of contralateral eyes in a cohort of Asian patients presenting with unilateral tAMD or PCV. This is comparable to previous studies in white populations that reported nonexudative neovascularization could be visualized in 11% (46/432) eyes with ICGA\(^5,6,10\) and 27% (3/11 eyes) using OCT-A.\(^9,10\)

A previous study investigated the detection rate for quiescent neovascularization using other OCT-A instruments on a white population and reported a high sensitivity (81.8%) and specificity (100%) for quiescent CNV detection.\(^7\) In the current study, however, most of the nonexudative neovascularization lesions were identified based on ICGA. Optical coherence tomography angiography identified flow signal in only 3 of 10 eyes with ICGA features suggestive of nonexudative neovascularization. Although there is a debate, neovascularization in PCV are thought to originate from the inner choroid and penetrate Bruch’s membrane.\(^27,28\) In support of this idea, recent studies clarified that polypoidal lesions are located in the sub-RPE space or inner choroid or both.\(^29–31\) Therefore, it is possible that neovascularization visualized only by ICGA, but not by OCTA, is abnormal blood vessels located in the inner choroid that are difficult to be visualized by the currently commercially available OCT-A instruments. Alternatively, slow flow velocity within neovascularization network may explain why the lesion is more readily detected by ICGA than using OCTA. Needless to say, the difference may be due to the different acquisition protocol used to acquire OCT-A images. It should be noted, however, OCTA identified possible neovascularization in an additional four eyes that did not have plaques on ICGA. The reason behind the discrepancy between ICGA and OCT-A remains to be evaluated. A possible explanation would be the presence of CVH that might have masked plaque detection in the late frame of ICGA. Indeed, two of four cases in which neovascularization was detected only using OCT-A had CVH (Fig. 3). It is also important to note that pachychoroid neovascularopathy appears as hypercyanescent neovascular network in early phase of ICGA and late phase of ICGA is characterized by wash-out of the quiescent CNV.\(^8\) As discussed below, nonexudative neovascularization lesions in the current cohort may be related...
to pachychoroid neovasculopathy and not to AMD. Together with these previous studies, current findings suggest that OCT-A can be an important complement to the diagnosis of nonexudative neovascularization, although it cannot replace ICGA.

In the current series, CVH and pachyvessels were seen in a significant proportion of eyes with tAMD. Although other series have reported CVH may be present in as high as 40% in eyes with tAMD,14,32–38 the high prevalence of CVH in the current study may reflect that tAMD in the Asian populations may have different characteristics compared with the white population. We assume that we have more patients in the tAMD group complicated by a “central serous chorioretinopathy” background presumably due to environmental factors. Hence, substantial proportion of nonexudative neovascularization in the current cohort may be nonexudative pachychoroid neovascularopathy, and thus less related to AMD. Pachychoroid phenotype is believed to result from functionally and anatomically abnormal choroidal vessels, and the most salient features include presence of dilated vessels (“pachyvessels”) in the Haller’s layer, and CVH presumably due to hyperpermeable choroid. In the current study, we also evaluate pachychoroid in the fellow eyes of patients with tAMD and PCV and identified a significant association between pachychoroid pigment epitheliopathy, but not pachyvessels alone, and nonexudative neovascularization. Pachychoroid neovasculopathy19 together with pachychoroid pigment epitheliopathy,18 belong to the pachychoroid spectrum of diseases. Indolent pachychoroid neovascularization has also been detected in the eyes with pachychoroid spectrum diseases, such as chronic central serous chorioretinopathy39–41 and within shallow irregular pigment epithelial detachment in pachychoroid spectrum disease.42 In the current cohort of Asian patients, we report that pachychoroid pigment epitheliopathy, diagnosed in the presence of undulating RPE line with or without shallow pigment epithelial detachment on OCT in an area where the underlying choroid was thickened or exhibited pachyvesels,18 was associated with presence of nonexudative neovascularization.

Previous studies have reported that presence of both drusen and pigmentary abnormalities are risk factors for developing exudative AMD.43 The findings from the current study further point toward focal or generalized choroidopathy as a potential underlying cause of the RPE atrophy noted. We were able to demonstrate that areas of neovascularization were closely associated with areas of underlying pachyvessels and localized disturbance in choriocapillaris flow signal on OCT-A was also seen in a significant number of eyes. This is in line with previous studies that demonstrated inward displacement of deep choroidal vessels due to pachyvessels, and concomi-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>tAMD, n = 33</th>
<th>PCV, n = 43</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonexudative neovascularization</td>
<td>8 (24%)</td>
<td>6 (14%)</td>
<td>0.197*</td>
</tr>
<tr>
<td>Any drusen</td>
<td>23 (69%)</td>
<td>22 (51%)</td>
<td>0.157*</td>
</tr>
<tr>
<td>Reticular pseudodrusen</td>
<td>9 (27%)</td>
<td>4 (9.3%)</td>
<td>0.065*</td>
</tr>
<tr>
<td>Choroidal vascular hyperpermeability</td>
<td>17 (52%)</td>
<td>14 (32%)</td>
<td>0.107*</td>
</tr>
<tr>
<td>Pachychoroid pigment epitheliopathy</td>
<td>16 (48%)</td>
<td>20 (47%)</td>
<td>0.385*</td>
</tr>
<tr>
<td>Choroidal thickness (µm)</td>
<td>226 (110)</td>
<td>223 (97)</td>
<td>0.876†</td>
</tr>
</tbody>
</table>

Pachyvessels, assessed by:
- ICG: 20 (61%) vs. 20 (47%), P = 0.253*
- OCT: 30 (91%) vs. 33 (76%), P = 0.131*
- OCT-A: 25 (76%) vs. 31 (72%), P = 0.797*
- Any 1 of above modes: 30 (91%) vs. 36 (83%), P = 0.499*
- All 3 modes: 15 (46%) vs. 17 (40%), P = 0.645*

* P value by Fisher exact test.
† P value by t-test.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Neovascularization (−), n = 62</th>
<th>Neovascularization (+), n = 14</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis (tAMD, %)</td>
<td>25 (40%)</td>
<td>8 (57%)</td>
<td>0.371†</td>
</tr>
<tr>
<td>Any drusen</td>
<td>35 (56%)</td>
<td>10 (71%)</td>
<td>0.376†</td>
</tr>
<tr>
<td>Reticular pseudodrusen</td>
<td>12 (19%)</td>
<td>1 (7.1%)</td>
<td>0.441†</td>
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<tr>
<td>Choroidal vascular hyperpermeability</td>
<td>22 (35%)</td>
<td>9 (64%)</td>
<td>0.070†</td>
</tr>
<tr>
<td>Pachychoroid pigment epitheliopathy</td>
<td>23 (37%)</td>
<td>13 (93%)</td>
<td>0.0001†</td>
</tr>
<tr>
<td>Choroidal thickness (µm)</td>
<td>222 (99)</td>
<td>233 (117)</td>
<td>0.618‡</td>
</tr>
</tbody>
</table>

Pachyvessels, assessed by:
- ICG: 29 (47%) vs. 11 (79%), P = 0.040† |
- OCT: 49 (79%) vs. 14 (100%), P = 0.110† |
- OCT-A: 43 (69%) vs. 13 (93%), P = 0.097† |
- Any 1 of above modes: 52 (88%) vs. 14 (100%), P = 0.192† |
- All 3 modes: 22 (35%) vs. 10 (71%), P = 0.018† |

* P value by Multinominal logistic regression.
† P value by Fisher exact test.
‡ P value by t-test.
tant attenuation of choriocapillaris and Sattler layer in pachychoroid spectrum diseases. Thus, the current study supports the idea that pachyvessels compress the inner choroid, and cause circulatory disturbances in the setting of pachychoroid spectrum diseases.

We are aware of the limitation of current study mainly due to a relatively small number of patients from a single institution and the relatively narrow scan area of the OCT-A used in the current study. The prevalence of drusen and RPD was not significantly different between the tAMD group and the PCV group in the current cohort, but may be due to limited sample size. The choroidal thickness between the tAMD group and PCV group was not different, which may reflect the fact that substantial proportion of eyes with tAMD had CVH in the current cohort. The subgroup of eyes with RPD ($n = 13$) may be more representative of tAMD, and indeed had significantly thinner choroid and higher prevalence of drusen. Lastly, future longitudinal study will be needed to evaluate the temporal relationship between these choroidal vascular abnormalities and exudative AMD, and whether a cause and effect relationship exists between them.

In conclusion, our study demonstrated that combination of ICGA and OCT-A can identify nonexudative neovascularization in up to 18% of contralateral eyes in a cohort of Asian patients presenting with unilateral tAMD or PCV. Presence of pachychoroid epitheliopathy should alert clinicians to the possibility of underlying neovascularization. Large natural history studies are needed to characterize clinical significance of nonexudative neovascularization. Factors that lead to frank exudation in these eyes, if identified in future, will have important therapeutic implications.

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