Polypoidal choroidal vasculopathy (PCV), first described by Yannuzzi et al.,\textsuperscript{1} consists of a branching vascular network (BVN), with polypoidal lesions at its edge, under the retinal pigment epithelium (RPE).\textsuperscript{1,2} Polypoidal choroidal vasculopathy is a disease characterized by multiple, recurrent serosanguineous detachments of the RPE and neurosensory retina, associated with secondary bleeding or leakage from the polypoidal lesions.\textsuperscript{3–6}

Polypoidal choroidal vasculopathy diagnosis is based on ophthalmoscopic identification of subretinal reddish orange spheroidal lesions arising from choroidal vessels.\textsuperscript{1} Indocyanine green angiography (ICGA) demonstrates polypoidal dilatations at the terminals of the BVN.\textsuperscript{5,7–10}

In eyes with PCV, optical coherence tomography (OCT) shows highly elevated RPE or double reflective layers that consist of RPE and another highly reflective layer beneath the RPE ("double-layer sign") in the area of the BVN.\textsuperscript{11}

Yannuzzi et al.\textsuperscript{1} have described PCV as a primary abnormality of the choroid. Yuzawa et al.\textsuperscript{12} have noted that PCV is caused by inner choroidal vessel abnormalities, not choroidal neovascularization (CNV). However, recent studies with high-resolution OCT have demonstrated that polypoidal lesions exist beneath the RPE, indicating that PCV is a variant of type 1 neovascularization (NV)\textsuperscript{13,14}, and Kawamura et al.\textsuperscript{14} report that there are two types of PCV: polypoidal CNV and typical PCV, which shows choroidal vessel abnormalities. Despite a number of these studies, pathogenesis of PCV is not fully understood.

En face OCT angiography (OCTA) is the novel technology that can visualize chorioretinal microcirculation without intravenous dye injection.\textsuperscript{15–24} And OCTA also allows us to do three-dimensional analysis of the chorioretinal abnormal lesions.

In this study we compared the angiographic features of PCV detected by ICGA and OCTA, and using B-scan OCTA images, we also did three-dimensional analysis to find the location of the polypoidal lesions and the BVN to understand the pathogenesis of PCV.

METHODS

Patients

This study was a retrospective chart review of patients who had undergone fundus examination, including OCTA, at Nagoya City University Hospital between December 2014 and January 2016.

Twenty eyes with a clinical diagnosis of treatment-naive PCV were evaluated. This study was approved by the Institutional Review Board of the Nagoya City University Graduate School of Medical Science and was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki. Eyes with poor-quality OCT images due to cataract or poor fixation were excluded from the study.

The diagnosis of PCV was based on ophthalmoscopic examinations, ICGA, high-definition (HD) OCT (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA, USA), and swept-source
OCT (DRI OCT-I Atlantis; Topcon Medical Systems, Oakland, NJ, USA) and OCTA. Indocyanine green angiography was performed by using Heidelberg Retina Angiograph 2 (HRA2; Heidelberg Engineering, Heidelberg, Germany). Optical coherence tomography angiography was performed by using Avanti RTVue XR with AngioVue (Optovue, Inc., Fremont, CA, USA). Optical coherence tomography angiography and ICGA were performed on the same day.

We counted the number of polypoidal lesions and the BNVs in each ICG angiogram and OCT angiogram, and the detection rate for each lesion was compared. Using OCTA, we evaluated the relationship in the location between polypoidal lesions and pigment epithelial detachment (PED), and also did three-dimensional analysis of the location of the BNV.

**En Face OCTA**

Optical coherence tomography angiography was performed with Avanti RTVue XR with AngioVue. AngioVue uses the split-spectrum amplitude decorrelation angiography (SSADA) algorithm to detect erythrocytes’ movement, and this software allows us to visualize noninvasively the retinal and choroidal vasculature via motion contrast. AngioVue (AngioAnalytics) was used to measure the area and flow area to follow the size of the polypoidal lesions before and after treatment.

**Statistics**

All results are expressed as the mean ± SD. Data were collected and analyzed by the paired t-test. For all statistical tests, \( P < 0.05 \) was considered as the significance level. Statistical analysis was performed by using Ekuseru-Toukei 2012 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

**RESULTS**

Demographics of patients with PCV are shown in the Table. Twenty eyes of 20 patients (18 male, 2 female) were evaluated in this study. Average age was 71.9 ± 9.8 years (range, 54–95 years). All eyes had dilated choroidal vessels or thickened choroid detected by ICGA or swept source (SS)-OCT, and all cases were considered as typical PCV.

The polypoidal lesions were detected in 20 eyes (100%) by ICGA, and in 17 eyes (85%) by OCTA. The number of polypoidal lesions detected by OCTA averaged 2.6 ± 1.9, and 2.0 ± 1.1 by ICGA (\( P < 0.05 \)).

Manual segmentation was required to detect the pathologic lesions of PCV in all cases. From analysis combined with the images of OCT longitudinal scan (B-scan) and OCTA, we determined that polypoidal lesions were located inside elevated RPE lesions without fluid (six eyes), at the margin of serous PED (five eyes), or inside of serous PED (nine eyes). The BNV was detected in 14 eyes (70%) by ICGA and in 14 eyes (70%) by OCTA.

**TABLE. Clinical Characteristics of Patients With PCV and Their ICGA and OCTA Findings**

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age, y</th>
<th>Eye</th>
<th>LogMAR VA</th>
<th>ICGA Presence of Polypoidal Lesions (No.)</th>
<th>OCTA Presence of Polypoidal Lesions (No.)</th>
<th>Relationship in Location Between Polypoidal Lesions and PED</th>
<th>Presence of BNV</th>
<th>Location of BNV</th>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>80</td>
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<td>+ (3)</td>
<td>+ (3)</td>
<td>Inside PED</td>
<td>+</td>
<td>Between BM and CC</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>76</td>
<td>L</td>
<td>0.523</td>
<td>+ (1)</td>
<td>+ (1)</td>
<td>No PED</td>
<td>+</td>
<td>Between BM and CC</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>77</td>
<td>L</td>
<td>−0.079</td>
<td>+ (3)</td>
<td>+ (&gt;5)</td>
<td>Inside PED</td>
<td>+</td>
<td>Between BM and CC</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
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<td>L</td>
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<td>+ (1)</td>
<td>+ (1)</td>
<td>Margin of PED</td>
<td>+</td>
<td>Between BM and CC</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>74</td>
<td>L</td>
<td>0.301</td>
<td>+ (1)</td>
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<td>Inside PED</td>
<td>+</td>
<td>Between BM and CC</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>67</td>
<td>L</td>
<td>−0.176</td>
<td>+ (2)</td>
<td>+ (1)</td>
<td>Margin of PED</td>
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<td>–</td>
</tr>
<tr>
<td>7</td>
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<td>L</td>
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<td>–</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
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<td>R</td>
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<td>+ (3)</td>
<td>+ (3)</td>
<td>Inside PED</td>
<td>+</td>
<td>Between BM and CC</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>77</td>
<td>L</td>
<td>0.046</td>
<td>+ (5)</td>
<td>+ (6)</td>
<td>No PED</td>
<td>+</td>
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</tr>
<tr>
<td>10</td>
<td>M</td>
<td>70</td>
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<td>0.155</td>
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<td>+ (1)</td>
<td>No PED</td>
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</tr>
<tr>
<td>11</td>
<td>M</td>
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<td>L</td>
<td>0.000</td>
<td>+ (1)</td>
<td>+ (2)</td>
<td>Margin of PED</td>
<td>+</td>
<td>Between BM and CC</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
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<td>R</td>
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<td>+ (2)</td>
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</tr>
<tr>
<td>13</td>
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<td>–</td>
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<tr>
<td>14</td>
<td>M</td>
<td>67</td>
<td>L</td>
<td>0.097</td>
<td>+ (2)</td>
<td>+ (2)</td>
<td>Inside PED</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>63</td>
<td>L</td>
<td>0.097</td>
<td>+ (2)</td>
<td>+ (5)</td>
<td>Margin of PED</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
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<td>R</td>
<td>−0.176</td>
<td>+ (5)</td>
<td>+ (3)</td>
<td>Inside PED</td>
<td>+</td>
<td>Between BM and CC</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>54</td>
<td>L</td>
<td>0.097</td>
<td>+ (1)</td>
<td>+ (3)</td>
<td>Inside PED</td>
<td>+</td>
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</tr>
<tr>
<td>18</td>
<td>M</td>
<td>58</td>
<td>L</td>
<td>0.000</td>
<td>+ (1)</td>
<td>+ (2)</td>
<td>Margin of PED</td>
<td>–</td>
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<tr>
<td>19</td>
<td>M</td>
<td>81</td>
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<td>0.523</td>
<td>+ (3)</td>
<td>+ (4)</td>
<td>Inside PED</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>83</td>
<td>L</td>
<td>0.222</td>
<td>+ (2)</td>
<td>+ (4)</td>
<td>Inside PED</td>
<td>+</td>
<td>Between BM and CC</td>
</tr>
</tbody>
</table>

M, male; F, female; VA, visual acuity; L, left; R, right; BNV, branching vascular network; PED, pigment epithelial detachment; BM, Bruch’s membrane.
eyes (70%) by OCTA. All of the BVNs detected by OCTA were located between the RPE and Bruch’s membrane (BM).

Case 1

A 65-year-old man came to our hospital for a distortion in vision in his left eye of a few weeks’ duration. Visual acuity was 20/20 in both eyes. Fundus examination revealed PED with subretinal hemorrhage (Fig. 1A). Early-phase ICGA showed the polypoidal lesion (yellow arrowhead) inside the PED and BVN (yellow circle) (B). Optical coherence tomography B-scan shows serous retinal detachment and two highly reflective layers consisting of RPE and another reflective layer beneath the RPE (“double-layer sign”) (white circle) (C). The polypoidal lesions and the BVN are not detected on OCTA taken by autosegmentation mode (D1, D2). The polypoidal lesion is clearly seen on OCTA, and the corresponding B-scan taken by manual-segmentation mode shows the polypoidal lesions (yellow arrowhead) inside the PED detached from Bruch’s membrane (E1, E2). Optical coherence tomography angiography shows the BVN (yellow circle) clearly, and the corresponding B-scan reveals the BVN between the RPE and above the highly reflective layers, supposedly Bruch’s membrane (white circle) (F1, F2).

Case 2

A 70-year-old man complained of acute deterioration in his right vision. Visual acuity was 20/32 in his right eye. Fundus examination revealed reddish orange nodules with subretinal hemorrhage (Fig. 2A). Early-phase ICGA showed the BVN terminating in the polypoidal lesion (Fig. 2B). The polyps and the BVN were clearly seen on OCTA (Figs. 2C1, 2C2, 2D1). The BVN was located between the RPE and BM (Fig. 2D2).

Case 3

An 80-year-old woman was referred to our hospital with PCV. Visual acuity was 20/25 in her left eye. Early-phase ICGA showed multiple polyps (Fig. 3A). Using OCTA, one polyp was clearly detected, but the other polyps were poorly identified (Fig. 3C1, 3C2). The BVN was clearly detected on OCTA (Fig. 3D1, 3D2).
Case 4

A 77-year-old man was referred to our clinic with diagnosis of PCV (Fig. 4A). Visual acuity was 20/25 in his left eye. The size of the polyp and the flow area inside the polyp lesion was followed up before and after anti-VEGF treatment. The same scanning slab was used to analyze the polyp lesion during follow-up. The size of the polyp lesion was 0.148 mm² and the flow area was 0.093 mm² before treatment. Thirty days after injection of anti-VEGF agent, the patient’s vision achieved 20/20, and the size of the same polyp was decreased to 0.076 mm² with the disappearance of subretinal fluid. The flow area was also decreased to 0.053 mm² (Fig. 4B). Four months later after two injections, the size of the same polyp and the flow area were increased to 0.118 and 0.074 mm² (Fig. 4C) with recurrence of subretinal fluid.

Discussion

Our current study compared the angiographic features of PCV detected by ICGA and OCTA. Our results demonstrated that the detection rate of the polypoidal lesions was significantly low by OCTA compared with ICGA, but the BVN was clearly detected by OCTA as well as by ICGA. Moreover, from combined analysis with OCT B-scan and OCTA, the BVN was observed to be located between the RPE and Bruch’s membrane.

Optical coherence tomography angiography is a newly developed method, which can visualize chorioretinal circulation without dye injection. Optical coherence tomography angiography has already been applied to various retinal vascular diseases, and it is reported that OCTA is useful to detect abnormal vascular lesions.16–18,26 Recently, Inoue et
al. have evaluated the spectrum of PCV by using OCTA. They have observed case series of seven patients with PCV or polypoidal CNV, with six of seven patients receiving previous treatment. They report that OCTA provides anatomic information about the BVN and type 1 NV, which is comparable to ICGA. However, the polyps are visualized in only three of seven cases (42.9%) by OCTA. In our current study, the polypoidal lesions were detected in 17 of 20 eyes (85%) by OCTA, and the detection rate was higher than that reported by Inoue et al. Using OCTA, the polyps were not visualized in some cases, possibly owing to the poor blood flow in the polyp, since OCTA can detect the blood flow, but not the vessels themselves. All our cases included treatment-naïve PCV, and Inoue et al. have included the eyes with previous treatment in their study. Since anti-VEGF treatment or photodynamic therapy induces the regression of the polyp, the previous history of treatment might reduce the detection rate by OCTA. Another point is that staining or pooling of ICGA dye around the polyps enhances the visualization of the polyps in ICGA in the late phase. Miura et al. have reported that polypoidal lesions in the Doppler OCT images are clearly detected at the corresponding locations of the lesions in the ICGA images, but the polyps visualized by Doppler OCT are much smaller than those detected by ICGA, which indicates that the real size of the polyps is smaller. Since the axial resolution is 5 μm in OCTA, OCTA might not be able to detect small polyps.

As for the anatomic location of the polyps and the BVN, Inoue et al. have reported that the BVN, type 1 NV, and the

**Figure 3.** Multimodal imaging of an 80-year-old woman. Early-phase ICGA shows multiple polyps (yellow arrowhead) (A). One polyp is clearly detected (yellow arrowhead) but the others are poorly detected on OCTA (yellow dot circle) (C1). The polyps are located at the level of Bruch’s membrane on corresponding B-scan (C2). The BVN (yellow circle) is clearly detected on OCTA (D1). Corresponding B-scan shows the BVN located between the RPE and Bruch’s membrane (white circle) (D2).
polyps are confined to the anatomic compartment between the RPE and BM. In our current study, all of the BVNs and the polyps detected by OCTA were located between the RPE and BM. Our results are compatible with a previous report by Inoue et al., and our findings may support the idea that PCV is a variant of type 1 NV. Studies with large numbers of cases will be required, but with OCTA and OCT B-scan, the pathophysiology of PCV may be more clearly understood in the future.

Since ICGA can visualize choroidal vasculature, ICGA has been the gold standard diagnostic tool for PCV. Although ICGA is considered safe, intravenous dye has risks ranging from discomfort, to nausea, to anaphylaxis in rare cases. In addition, owing to time-consuming issues, performing ICGA at each clinical visit is not practical in daily practice.

In our study, the size of the polyp and the flow area inside the polyp lesion were followed up before and after anti-VEGF treatment with a measuring tool (AngioAnalytics). Because we can evaluate the polypoidal lesions and the BVN at each clinical visit, using OCTA without dye injection might be useful to monitor the progression or recurrence during follow-up. However, ICGA would still be necessary in diagnosing PCV, since the detection rate of the polypoidal lesions was significantly low by OCTA compared with ICGA.

The current study had several limitations. This study was a retrospective case series with a limited number of patients, so further study with a prospective study design in a larger number of patients will be required.

In conclusion, despite the manual segmentation required, en face OCTA enabled us to analyze the angiographic features of PCV combined with OCT B-scan. Indocyanine green angiography will still be necessary to make the diagnosis of PCV. En face OCTA may be useful for understanding the pathogenesis of PCV and managing PCV.

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References