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Time course of swept-source optical coherence tomography angiography findings after photodynamic therapy and aflibercept in eyes with age-related macular degeneration

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ABSTRACT

Purpose: To report swept-source optical coherence tomography angiography (SS-OCTA) findings after full-fluence photodynamic therapy (PDT) and aflibercept intravitreal injection (IVA) for age-related macular degeneration (AMD).

Methods: Five eyes of five patients with AMD treated with PDT and IVA were include into the study. We retrospectively reviewed the data obtained from the five patients using SS-OCTA before and after treatment. Three eyes had type 1 choroidal neovascularization (CNV) and two eyes had polypoidal choroidal vasculopathy.

Results: Before treatment, the CNV signals detected in all cases, decreased in three eyes and were not detected completely in two eyes at 1 months after treatment. The areas indicating CNV increased over time, but they did not increase to the baseline level. No CNV signal was detected in one eye during follow-up. In all cases, the exudation unchanged or resolved without additional IVA; the exudation recurred in two cases. In one eye, the CNV signal and the exudation occurred simultaneously; however, there was no association in another eye. A feeder vessel, from which the CNV signal seemed to originate, was seen in one of the five eyes.

Conclusion and Importance: SS-OCTA is useful to monitor the morphology of CNV after PDT and IVA, indicating that the remodeling of the choroidal vasculature occurs gradually after treatment. The presence or absence of the CNV signal might indicate CNV activity.

1. Introduction

Age-related macular degeneration (AMD) is the third leading cause of blindness worldwide and the primary leading cause of visual loss in the Western world.[1] Recently, anti-vascular endothelial growth factor (VEGF) therapy has become the primary treatment for wet AMD based on the results of various clinical trials.[2–4] Before the introduction of anti-VEGF therapy, photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis AG, Basel, Switzerland) had been the first-line treatment, and it is still used in cases with polypoidal choroidal vasculopathy (PCV) and those refractory to and/or with tachyphylaxis to anti-VEGF drugs.[5–7]

Various examinations are necessary for AMD diagnosis and treatment. Generally, fluorescence angiography (FA) and indocyanine green angiography (ICGA) are used to establish the diagnosis, but it is difficult to repeat the examinations frequently because of the need for intravenous contrast agents. It also is difficult to observe the detailed morphology of choroidal neovascularization (CNV) due to dye leakage.[8] Optical coherence tomography (OCT) is another essential diagnostic tool for wet AMD and is indispensable for evaluating CNV activity.[9] Since it is a noninvasive examination, it can be performed repeatedly. However, since the examination provides cross-sectional images, it cannot be used to evaluate the extent and distribution of the CNV.

OCT angiography (OCTA) is a new imaging modality that enables visualization of the retinal and choroidal circulation without the need for an intravenous contrast agent.[10] The technology shows the retinal vasculature in each retinal slab and the choriocapillaris in a separate en-face image. Some studies that used OCTA have described choriocapillaris flow after PDT,[11–13] and Jung et al. reported the swept-source (SS) OCTA findings in the first month after application of PDT[14]; however, to the best of our knowledge, no report has described CNV remodeling after PDT with OCTA. In the current study, we retrospectively evaluated the time course of CNV remodeling after full-fluence PDT and intravitreal injections of aflibercept (IVA; Eylea, Bayer

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Yakuhin, Ltd., Osaka, Japan; Santen Pharmaceutical Co., Ltd., Osaka, Japan) for treating AMD.

2. Methods

2.1. Study design

The current study was an observational case series in which we retrospectively reviewed the records of patients who had been treated with PDT and IVA for wet AMD including type 1 CNV and PCV. The study was conducted at Osaka University Hospital from March 2018 through August 2018. The research adhered to the tenets of the Declaration of Helsinki. The institutional review board of Osaka University Hospital approved the study.

2.2. Diagnosis and management

The diagnosis of wet AMD was based on the characteristic findings on FA, ICGA (Spectralis, Heidelberg Engineering, Heidelberg, Germany), and OCT (DRI OCT-1 Atlantis, Topcon Corporation, Tokyo, Japan) images and fundus photographs. SS-OCTA (AngioPlex, Cirrus HD-OCT model 5000, Carl Zeiss Meditec, Dublin, CA) that was centered on the fovea was performed before and up to 3 months after the treatment. All patients were treated with verteporfin (6 mg/m^2 body surface area), according to the protocols of the Treatment of AMD with PDT studies.[5–7] The verteporfin was injected intravenously over 10 min followed by delivery of 50 J/cm^2 of a 689-nm laser light (Carl Zeiss Meditec) for 83 s. The greatest linear dimension (GLD) was measured on the FA images. The diameter of the PDT treatment spot size was the GLD plus 0 to about 1 mm. Combination therapy of IVA and PDT was applied in all cases. After topical anesthesia was applied, all patients were treated immediately after application of PDT with IVA (2.0 mg/0.05 ml) injected 3.5–4.0 mm posterior to the corneal limbus into the vitreous cavity using a 30-gauge needle.

Patients were excluded from this study if they had posterior abnormalities other than AMD that could affect observation with SS-OCTA and other imaging modalities. To evaluate the microvasculature of the CNV, macular cubes with a 3 × 3-mm scan patterns were used. This pattern included 245 A- and B-scans per 3 mm. To generate en-face images for the CNV analyses, we manually chose the boundaries from the lower edge of the outer nuclear layer to either the retinal pigment epithelium (RPE) or the line of Bruch's membrane if the RPE line was disrupted or elevated, as previously described.[15] The flow signal area of the CNV was measured manually using ImageJ software (National Institutes of Health, Bethesda, MD) on the SS-OCTA images.

3. Results

Table 1 shows the patient characteristics and the morphologic changes in the CNV on spectral-domain (SD) OCT and SS-OCTA images. The study included five eyes of five patients (3 men, 2 women; mean age, 73 ± 7.9 years). Three eyes had type 1 CNV and two eyes had PCV. The mean GLD was 2820 ± 950 μm (range, 2200–4700 μm). All eyes received aflibercept injections immediately after PDT was applied. All eyes had been treated previously with ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA) monotherapy, aflibercept monotherapy, and/or combination therapy of PDT plus aflibercept. No eyes needed retreatment during the follow-up period.

Before treatment, SS-OCTA visualized the microvasculature of the CNV in all cases. One month after treatment, SS-OCTA did not detect the CNV signal in two eyes and detected a partial CNV signal in three eyes. In one of two eyes in which the CNV was not detected (case 5), no signal was observed until the last follow-up observation, in another one eye (case 4), the CNV signal was detected 2 months after the treatment. In four eyes in which the CNV signal was detected (cases 1–4) until 3 months after treatment, the area indicating CNV increased gradually

Table 1
Patients characteristics and morphological change of CNV before and after PDT and IVA.

Case	Age (y.o.)	sex	R/L	AMD type	Previous treatments	GLD (microns)	BCVA				Exudative change on SDOCT				Size of CNV signal on SS-OCTA (%)				Connection of CNV and choroidal vessel
							Pre	1M	2M	3M	Pre	1M	2M	3M	Pre	1M	2M	3M	
1	80	F	R	Type 1	IVA, IVR, PDT + IVA	2500	0.045757	0.09691	NA	0.045757	+	±	NA	–	100	12	NA	40	–
2	81	M	R	Type 1	IVA	2200	0.154902	0.221849	NA	0.154902	+	+	NA	+	100	3	NA	30	+
3	73	M	R	PCV	IVA, IVR, PDT + IVA	4700	0	0.69897	0.522879	0.39794	+	+	–	+	100	15	70	85	–
4	59	F	R	Type 1	IVR, IVA	2500	0.045757	0.045757	0.09691	0.045757	+	–	+	+	100	0	51	50	–
5	72	M	L	PCV	IVA	2200	0	0	NA	0	+	–	NA	–	100	0	NA	0	–

GLD, greatest liner dimension; BCVA, best-corrected visual acuity; SDOCT, spectral domain optical coherence tomography; SSOCTA, swept-source optical coherence tomography angiography; CNV, choroidal neovascularization; PCV, polypoidal choroidal vasculopathy; IVA, intravitreal injection of aflibercept; IVR, intravitreal injection of ranibizumab; PDT, photodynamic therapy.

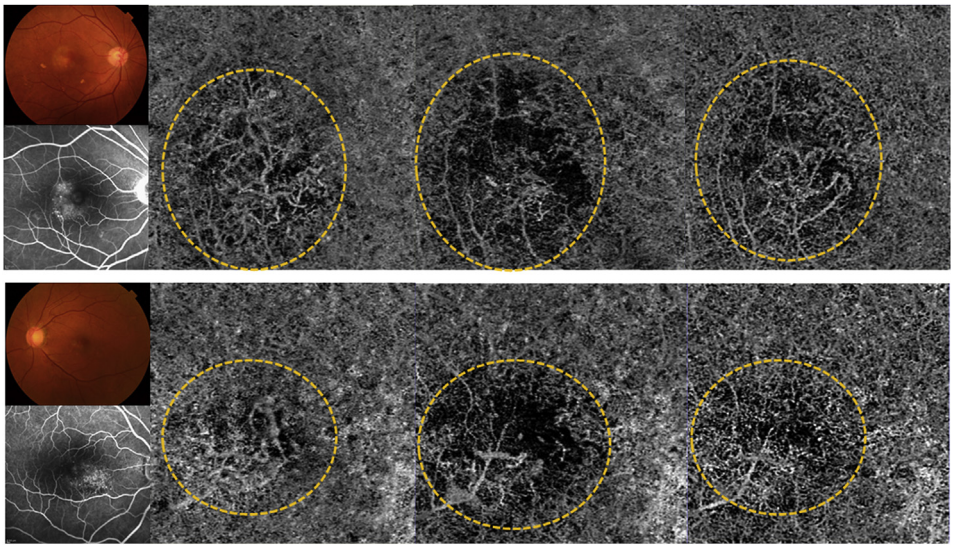

Fig. 1. The top row shows images obtained from an 80-year-old woman with type 1 choroidal neovascularization (CNV) who was treated with photodynamic therapy (PDT) and intravitreal aflibercept (IVA); a partial CNV signal is after PDT and IVA. The bottom row shows images obtained from a 72-year-old man with polypoidal choroidal vasculopathy who was treated with PDT and IVA; the CNV signal is undetected throughout the follow-up period (refer to Fig. 5). First row: (top) A fundus photograph and (middle) a fluorescein angiography image. Second row: (top) An en-face swept-source optical coherence tomography (SS-OCTA) image of the choriocapillaris layer before treatment with PDT and IVA shows the choriocapillaris flow around the CNV signal (circle). Third row: One month after treatment, SS-OCTA shows diminished choriocapillaris flow. Fourth row: Three months after treatment, SS-OCTA shows recovery of the choriocapillaris flow to the baseline level.

over time. In all four eyes, the area indicating CNV did not increase to the baseline level by the last follow-up examination; in the eyes with PCV (case 3), no signal was observed at the polyp lesion.

In all cases, the exudation did not change without additional IVA or resolve once during the follow-up period. The exudation recurred in two cases (cases 3, 4). There was no recurrence of exudation in one eye in which the CNV signal was not detected throughout the follow-up period (case 5). In case 4, there was no change in the exudation at 1 month when the CNV signal was not detected; the changes in the exudation recurred at 2 months after treatment when the CNV signal was detected. Among the three eyes in which the CNV signal was detected 1 month after the treatment, the change in the exudation recurred in one eye (case 3) and not in the other two (cases 1, 2).

Before treatment, a feeder vessel was observed in one of the five eyes, and the CNV signal presumably originated from that vessel (case 2).

The choriocapillaris circulation was impaired 1 month after PDT and IVA; it recovered to the baseline level within 3 months in all cases (Fig. 1).

CASE 2: An 81-year-old man received 23 IVA injections during the treat-and-extend regimen before treatment with PDT and IVA. The best-corrected visual acuity (BCVA) in his right eye was 20/30. Slit-lamp microscopy showed a few soft drusen and a CNV membrane with slight subretinal fluid (SRF) at the macula (Fig. 2). FA showed granular hyperfluorescence with late leakage, and ICGA visualized a CNV vascular network due to type 1 CNV. SD-OCT showed a fibrovascular pigment epithelial detachment (FV-PED) with slight SRF. En-face SS-OCTA provided better visualization of the CNV vascular network. After the patient provided informed consent, full-fluence PDT with a GLD of 2200 μm and IVA were administered. Until 3 months after treatment, SD-OCT showed a FV-PED with slight SRF at the same level as pretreatment without any additional IVA. En-face SS-OCTA images showed regression of the CNV signal; however, a partial signal was detected 1 month after treatment and gradually expanded over time. An SS-OCTA vertical scan showed the feeder vessel after treatment, and the CNV signal on SS-OCTA seemed to originate from that feeder vessel (Fig. 3).

CASE 3: A 73-year-old man received nine IVA injections, i.e., intravitreal ranibizumab three times and PDT and IVA twice before the current treatment with PDT and IVA. The BCVA in the right eye was 20/20. Slit-lamp microscopy showed a slight subretinal hemorrhage with a few soft drusen and a CNV membrane with slight SRF and hard exudates at the macula. FA showed granular hyperfluorescence with late leakage, and ICGA visualized a vascular network and polyp lesions. SD-OCT showed a PED with slight edema. En-face SS-OCTA provided better visualization of the vascular network, and the polyp lesions appeared as hyperreflective round lesions. After the patient provided informed consent, full-fluence PDT with a GLD of 4700 μm and IVA were administered. SS-OCTA showed a vascular network 1 month after treatment, and the signal expanded gradually until 3 months after treatment; no signal was seen at the polyp region. The exudation recurred 3

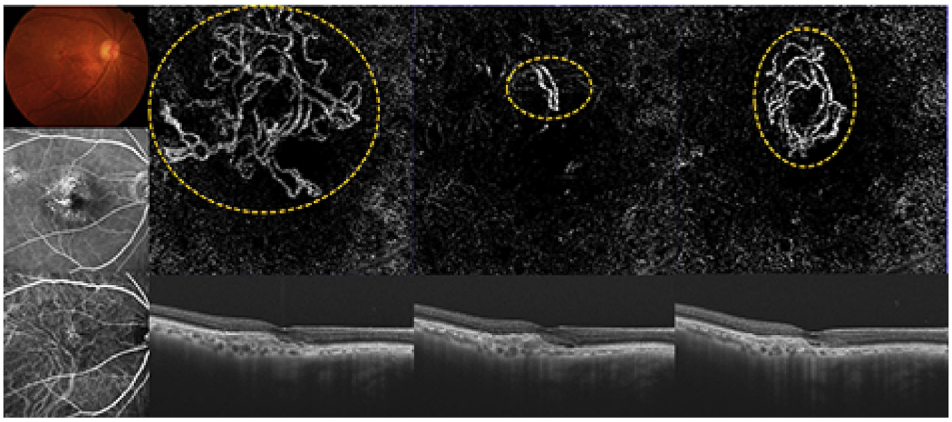

Fig. 2. An 81-year-old man with type 1 choroidal neovascularization (CNV) was treated with photodynamic therapy (PDT) and intravitreal aflibercept (IVA). *First row:* (top) A fundus photograph, (middle) fluorescein angiography, and (bottom) indocyanine green angiography show type 1 CNV at the macular. *Second row:* (top) An en-face swept-source optical coherence tomography (SS-OCTA) image and (bottom) a B-scan spectral-domain (SD) OCT image before treatment with PDT and IVA. An en-face SS-OCTA image shows the vascular network of type 1 CNV at the macula (circle). SD-OCT shows a fibrovascular pigment epithelial detachment (FV-PED) with slight subretinal fluid (SRF). *Third row:* One month after treatment, (top) SS-OCTA shows a regressed CNV signal and (bottom) SD-OCT shows a FV-PED with slight SRF at the same level as that at baseline. *Fourth row:* Three months after treatment, (top) SS-OCTA shows the gradual return of the CNV signal; however, (bottom) the SD-OCT image is the same as at 1 month. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

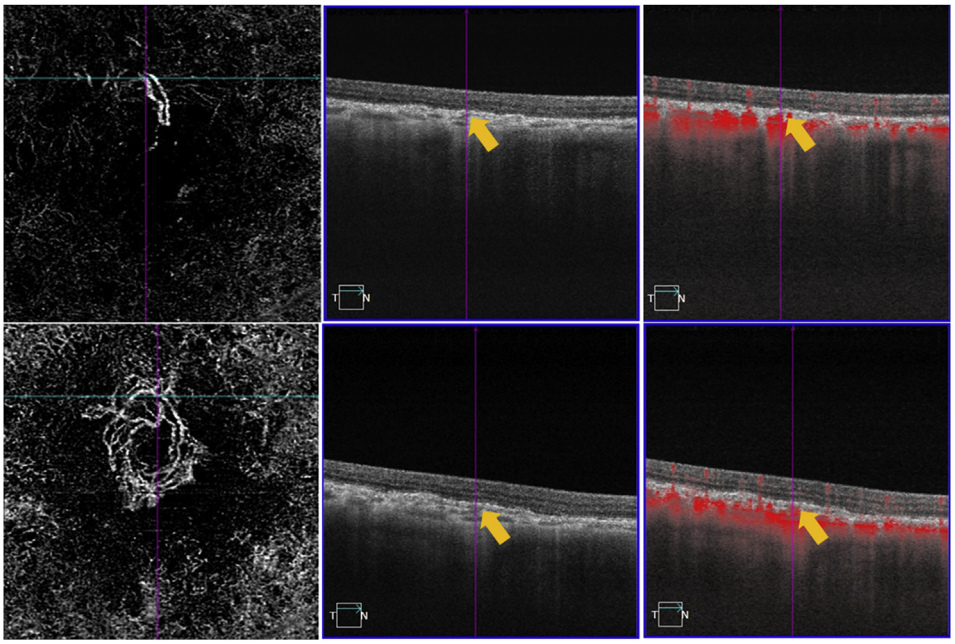

Fig. 3. The same case of in Fig. 2. (Left) An en-face swept-source optical coherence tomography (SS-OCTA) image, (middle) a B-scan image without and (right) with a flow signal. *First line:* One month after treatment, the connection between the choroidal neovascularization (CNV) and the choroid (feeder vessel) is seen on a B-scan image without flow signal (arrow) and that vessel has flow signal on a B-scan image with flow signal. The CNV signal on a SS-OCTA image seems to originate from that feeder vessel. *Second line:* At 3 months after treatment. The same feeder vessel as 1 month after treatment is seen on a B-scan image and the vessel has flow signal. The CNV signal on a SS-OCTA image seems to originate form that vessel.

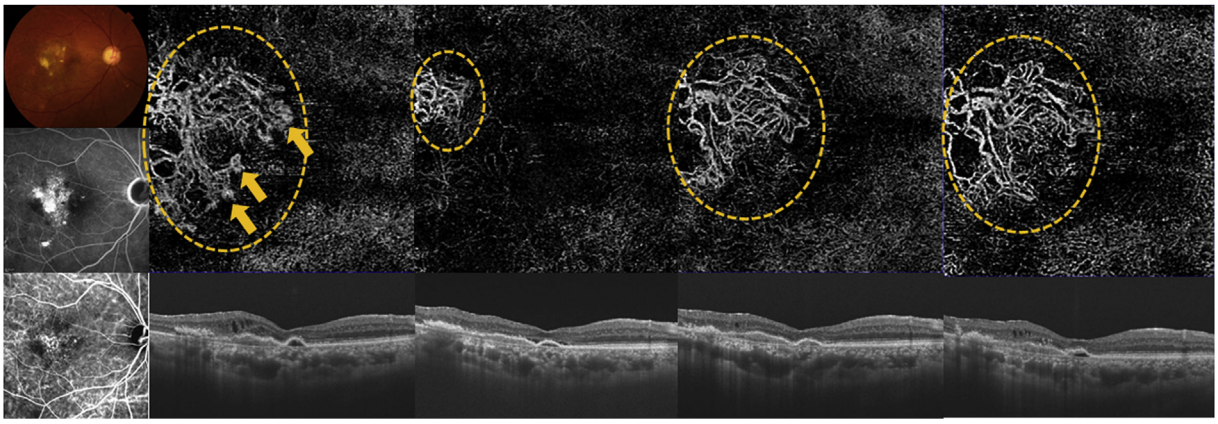

Fig. 4. A 73-year-old man with polypoidal choroidal vasculopathy (PCV) received photodynamic therapy (PDT) and intravitreal aflibercept (IVA). *First row:* (top) A fundus photograph, (middle) fluorescein angiography, and (bottom) indocyanine green angiography show PCV with a subretinal hemorrhage and hard exudates at the macula. *Second row:* (top) An en-face swept-source optical coherence tomography (SS-OCTA) image and (bottom) a spectral-domain (SD) OCT B-scan image before PDT and IVA. SS-OCTA shows the signal from the vascular network (circle), and the polyp lesions appear as round and hyperreflective (arrows). SD-OCT shows a pigment epithelial detachment (PED) with edema. *Third row:* One month after treatment, (top) SS-OCTA shows a regressed lesion in the vascular network. (bottom) SD-OCT shows a PED with slight subretinal fluid. *Fourth row:* Two months after treatment, (top) SS-OCTA shows the gradual expansion of the signal from the vascular network and SD-OCT shows (bottom) the dry retina. *Fifth row:* Three months after treatment, (top) SS-OCTA shows the gradual expansion of the signal from the vascular network and (bottom) SD-OCT shows recurrent edema. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

months after treatment (Fig. 4).

CASE 5: A 72-year-old man received 22 IVA injections during the treat-and-extend regimen before treatment with PDT and IVA. The BCVA in the left eye was 1.0. Slit-lamp microscopy showed a few soft drusen and a small PED with SRF at the macula. FA showed granular hyperfluorescence with late leakage, and ICGA visualized a vascular network and small polypoidal lesions due to PCV. SD-OCT showed a PED with SRF. En-face SS-OCTA provided better visualization of the vascular network; however, a polyp lesion was unclear. After the patient provided informed consent, full-fluence PDT with a GLD of 2200 μm and IVA were administered. SD-OCT showed regression of the PED without SRF until 3 months after treatment. En-face SS-OCTA did not show a CNV signal until the last follow-up period (Fig. 5).

4. Discussion

Several recent studies have reported OCTA findings before and after anti-VEGF therapy for AMD. Lumbroso et al. reported the morphology of the type 2 CNV changes after anti-VEGF therapy; the patterns of cyclic CNV varied during the follow-up period in a cycle of 62 days.[16] However, in the eyes with type 1 CNV, the flow density decreased significantly after treatment; however, the GLDs of the CNV are controversial.[17,18] Some investigators have reported that anti-VEGF therapy did not result in decreases in the size of the CNV, but another investigator reported that the size of the CNV decreased after anti-VEGF therapy.[16–18] Regarding PDT, to the best of our knowledge, few studies have used OCTA to longitudinally follow patients after PDT. Jung et al. used OCTA to observe one case of AMD with types 1 and 2 CNV before and after PDT and anti-VEGF therapy (bevacizumab, Avastin, Genentech Inc.) and reported significant resolution of type 2 CNV and

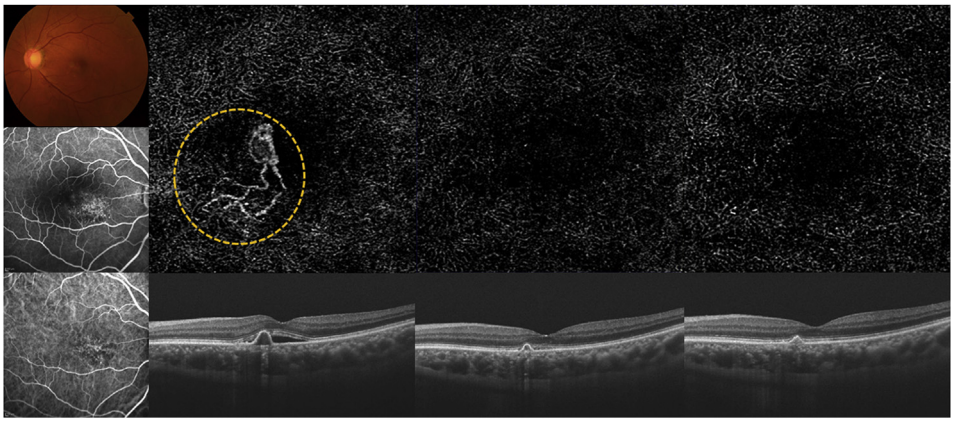

Fig. 5. A 72-year-old man with polypoidal choroidal vasculopathy (PCV) received photodynamic therapy (PDT) and intravitreal aflibercept (IVA). *First row:* (top) A fundus photograph, (middle) fluorescein angiography, and (bottom) indocyanine green angiography show PCV. No polyp lesions are observed. *Second row:* (top) An en-face swept-source optical coherence tomography (SS-OCTA) image and (bottom) a spectral-domain (SD) OCT B-scan image before treatment with PDT and IVA. SS-OCTA shows the signal from the vascular network (circle). SD-OCT shows a pigment epithelial detachment with subretinal fluid. *Third row and Fourth row:* (top) SS-OCTA shows no signal at both 1 month (first row) and (fourth row) 3 months after treatment. SD-OCT shows dry macular. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

decreased flow and size of type 1 CNV.[14] The current results showed the time course of OCTA findings in three cases with type 1 CNV and two cases with PCV before and after PDT and IVA. One month after treatment, the CNV signal decreased, and in two cases no CNV signal was seen on OCTA. Even 3 months after treatment, the CNV size remained smaller than that at baseline in four of the five cases, and in one case, the CNV signal was undetectable. Together with the results of the previous reports, we hypothesized that the response of CNV to PDT is stronger than the response to anti-VEGF therapy; however, since this report includes only five cases, further study with more cases is necessary to clarify this hypothesis.

In the current study, the exudation did not change without any additional treatment or resolve once in all cases and the exudation recurred in two of the five cases. In one eye, the exudation recurred at the same time as the CNV signal was detected; in another eye in which the CNV signal was detected just after treatment, the exudation disappeared once and then recurred. McClintic et al. noted that an increase in the CNV vessel area over time often resulted in exudation, but it was impossible to determine exactly when the exudation occurred; there seemed to be no association between the exudative changes and the presence or absence of the CNV signal.[19] In the current study, in one eye in which the CNV signal was undetected throughout the follow-up period, there was no recurrence of the exudation. Where no signal was detected, the exudation may not recur, and if so, OCTA might be an indicator of the recurrence of the exudation.

Recently, in eyes with myopic CNV, SS-OCT showed that the connection between the CNV and the scleral vessels mainly originated from the short posterior ciliary arteries.[20] Kuehlewein et al. reported that OCTA showed a large main feeder vessel in 75% of eyes with type 1 CNV.[21] In the current study, we found the feeder vessel in one of the five eyes, and the CNV signal was observed presumably originating from that vessel. Although there was no relationship between this feeder vessel and the short posterior ciliary arteries, the feeder vessel may be the origin of the CNV signal.

The choriocapillaris circulation was disrupted 1 month after PDT and IVA, and it recovered to the baseline level within 3 months in all cases. Several investigators have observed short-term choriocapillaris changes in central serous chorioretinopathy after half-dose PDT and reported that the choriocapillaris perfusion was diminished once after PDT and recovered at 1 month.[22,23] The recovery of the choriocapillaris circulation in the current study was slower than that reported previously presumably because of the different dosages of verteporfin and the different diseases. The disruption and recovery of the choriocapillaris were the same regardless of whether or not the CNV signal was detected during the follow-up period.

In conclusion, we observed five cases of AMD treated with PDT and IVA using SS-OCTA before and after administration of PDT and IVA. SS-OCT is a useful noninvasive technology for monitoring the morphology of AMD after PDT and IVA treatment. However, because all cases had a history of anti-VEGF therapy and/or PDT, as reported by Miere et al.,[24] the results may differ in treatment-naïve cases. Longer studies with more patients are necessary.

Patient consent

Patient consent was not obtained as all identifying patient information has been removed.

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All authors contributed significantly to the collection, writing, and/or critical review of the manuscript. The patients agreed to submission of this case study for publication.

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Conflict of interest

The following authors have no financial disclosures: (K.S., C.H., Y.F., S.S., H.S., K.N.)

Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

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