En Face Spectral-Domain Optical Coherence Tomography for the Diagnosis and Evaluation of Polypoidal Choroidal Vasculopathy

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BACKGROUND AND OBJECTIVE: To evaluate the diagnostic capability of en face spectral-domain optical coherence tomography (SD-OCT) in patients with polypoidal choroidal vasculopathy (PCV) diagnosed by indocyanine green angiography (ICGA).

PATIENTS AND METHODS: A retrospective, consecutive case series of 100 eyes diagnosed with PCV by ICGA were imaged with en face SD-OCT. Evaluation of the PCV complex on en face SD-OCT was performed on the ability to diagnose PCV by the characteristic configuration of the PCV complex and the extent and size of the PCV lesion.

RESULTS: The PCV complex was better visualized on ICGA in 45 eyes, on en face SD-OCT in 44 eyes, and equally well in 11 eyes. The extent of the PCV complex was larger on en face SD-OCT in 65 eyes, larger on ICGA in 23 eyes, and equal in size in 12 eyes.

CONCLUSION: En face SD-OCT images the characteristic findings of PCV and provides a noninvasive way to diagnose and treat PCV when ICGA is not available.

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INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) manifests clinically as a serosanguinous maculopathy, which can result in significant and progressive vision loss, and presents clinically very similar to neovascular age-related macular degeneration (NVAMD).[1] PCV is a variant of type I choroidal neovascularization (CNV) located between the retinal pigment epithelium (RPE) and Bruch's membrane.[2,3] Indocyanine green angiography (ICGA) is the gold standard for the diagnosis of PCV, without which the diagnosis is often missed.[4] However, ICGA is less frequently used due to its lack of availability in many clinics, more costly expense, and a lack of diagnostic expertise in ICGA evaluation in many parts of the world. Polypoidal choroidal vasculopathy is imaged on ICGA as a subretinal vascular structure with or without a branching vascular network (BVN) and aneurysmal dilations or polyps that are hyperfluorescent, and are often surrounded by a hypofluorescent halo.[5,6]

Polypoidal choroidal vasculopathy is becoming increasingly recognized and diagnosed internationally. In Asia, 20% to 50% of patients with serosanguinous maculopathy are typical of PCV.[7] It has also been previously reported in 4% to 14% of white patients.[8,9] However, recently in Brazil, Pereria et al. reported that 24.5% of their NVAMD patients had an ICGA diagnosis consistent with PCV in a

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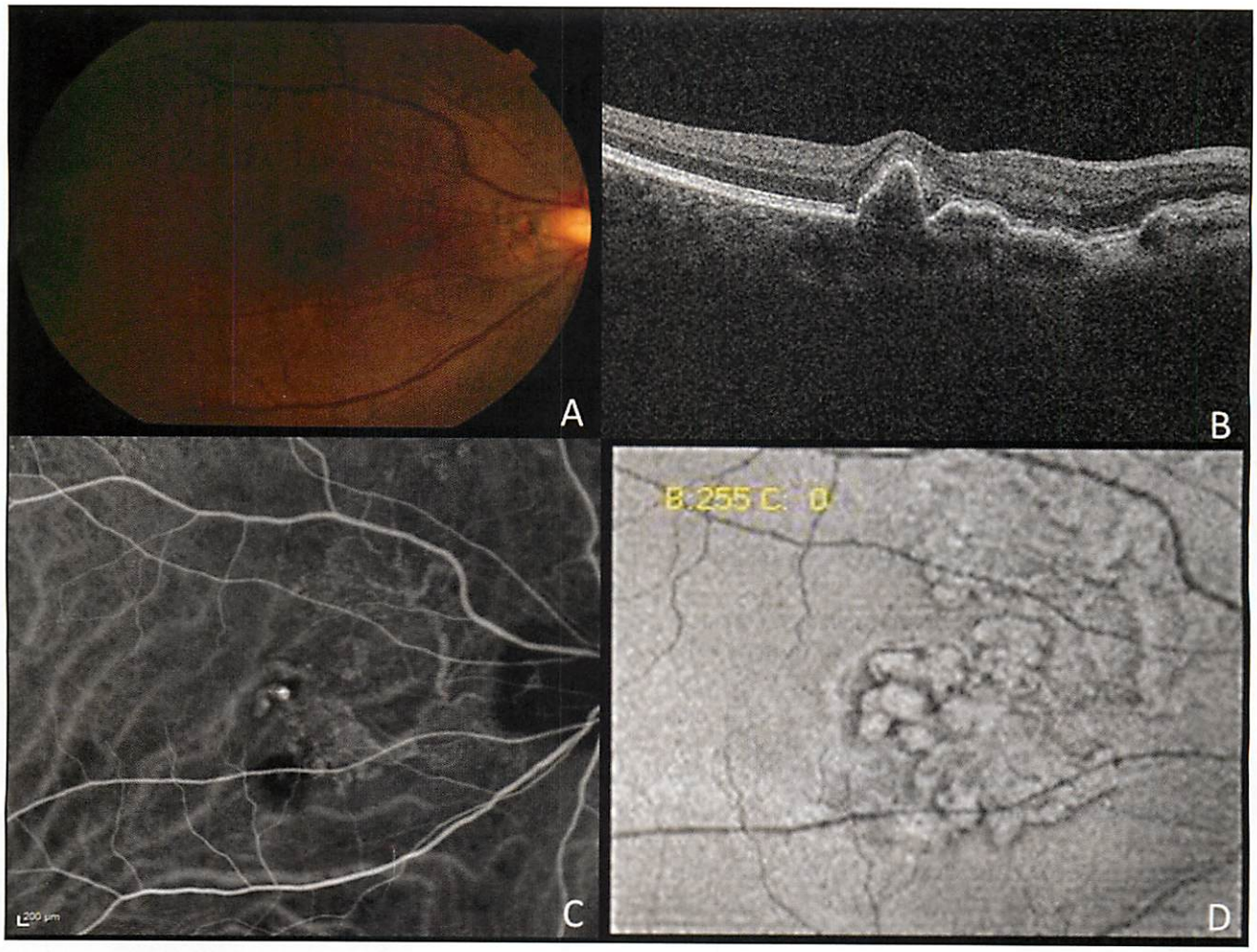

Figure 1. The polypoidal complex was better visualized on en face optical coherence tomography (OCT) than the corresponding indocyanine green angiography (ICGA) in this patient. (A) Fundus photo of a treatment-naïve right eye in an Asian female. (B) OCT line scan showing elevation of the retinal pigment epithelium (RPE) with polyps located beneath the RPE and above Bruch's membrane. (C) ICGA displaying the branching vascular network with saccular polypoidal dilations. (D) En face OCT with a dilated vascular structure with hyperreflective borders and polypoidal vascular dilations.

cohort with predominantly European ancestry.[10] In Switzerland, 21.5% of patients who had NVAMD resistant to anti-vascular endothelial growth factor (VEGF) therapy were actually PCV.[9]

The distinction between PCV and NVAMD is thus clinically important in clinical practice. The diagnosis of PCV can often be missed due to the infrequent use of ICGA. Polypoidal choroidal vasculopathy differs from NVAMD in clinical presentation, response to anti-VEGF therapy, and treatment paradigms.[8,11,12] Clinically, PCV more often presents with serous retinal detachment and less often with intraretinal edema than NVAMD.[13] There is a higher incidence of anti-VEGF resistance in PCV eyes.[13] Therapy also often includes photodynamic therapy (PDT) or combined PDT with intravitreal anti-VEGF therapy, which is much more successful at anatomically closing the polyps and decreasing the PCV complex than anti-VEGF therapy alone.[8,9,12,15]

The introduction of optical coherence tomography (OCT) technology has given insight into the structural changes and pathogenesis of PCV. Specifically, there are findings that are indicative of PCV on B-scan images on OCT. Polyps are defined by an inverted "U-shaped" elevation of the retinal pigment epithelium (RPE) with heterogeneous internal reflectivity.[2] PCV is often associated with a retinal pigment epithelial detachment (RPED) in which the PCV complex is localized as a notch in the RPED or attached to the elevated RPE within the RPED (icicle polyp).[2,3,14,15] The BVN has a characteristic appearance with a "double-layer sign" that is visualized as two parallel hyperreflective lines on

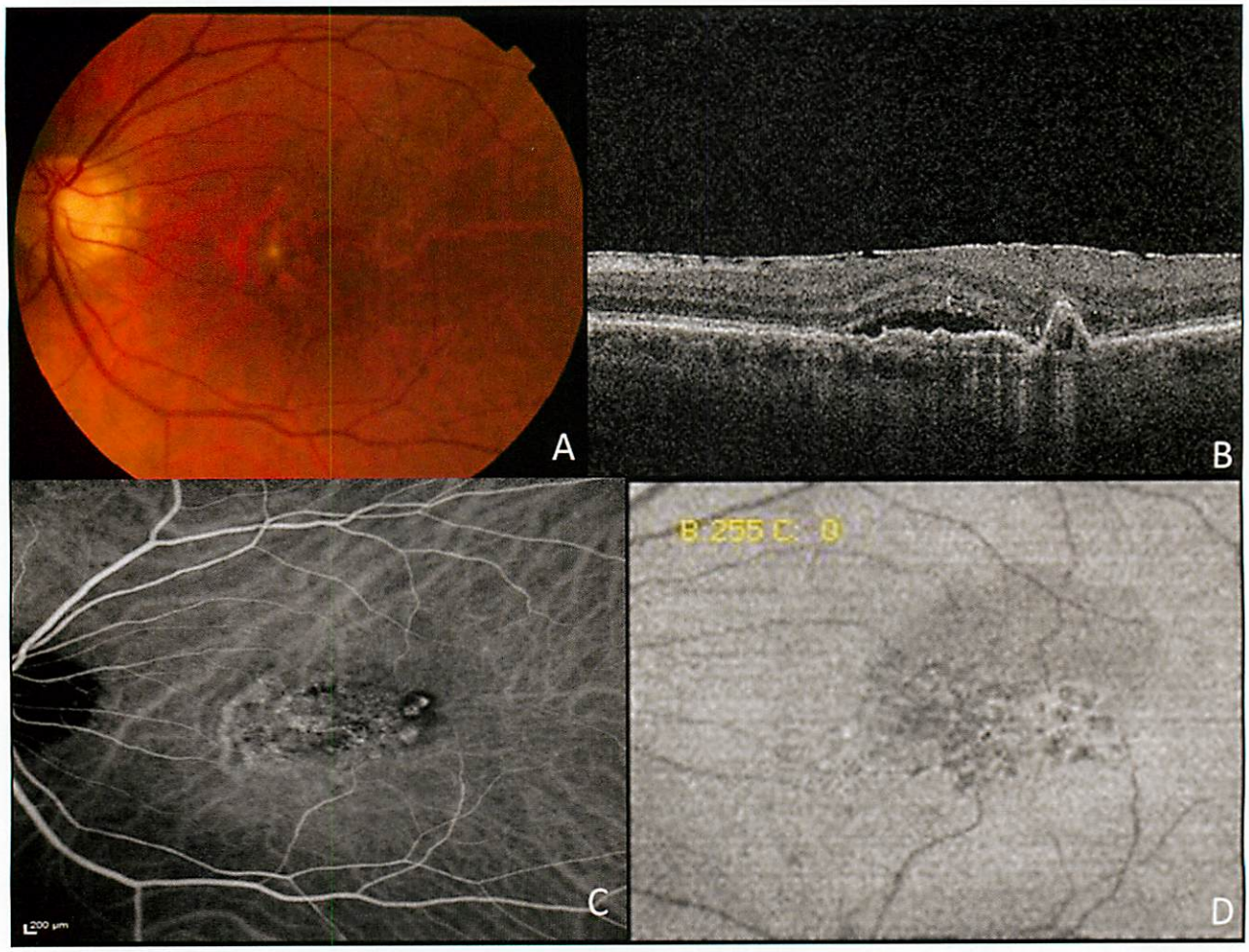

Figure 2. The polypoidal complex was better visualized on indocyanine green angiography (ICGA) than en face optical coherence tomography (OCT) in this patient. (A) Fundus photo of a treatment-naïve left eye in a white male. (B) OCT line scan showing elevation of the retinal pigment epithelium with a characteristic polyp with an adjacent branching vascular network (BVN) and subretinal fluid. (C) ICGA displaying the BVN and a temporal nodular polyp. (D) En face OCT displays hyperreflective and hyporeflective changes within the macula with little detail of the polypoidal complex.

OCT.[16,17] With the introduction of enhanced depth imaging OCT (EDI-OCT), a thicker choroid is observed in PCV patients.[18]

OCT has become the usual method to evaluate and follow treatment response in patients with exudative NVAMD, but usually involves evaluation of B scan images for subretinal fluid, intraretinal edema and subretinal fibrin or hemorrhage. En face OCT uses the same information already available through the conventional SD-OCT image, but presents the information in cross sectional images, which can be focused on different levels within the retina, under the retina and RPE, and within the choroid. Through en face OCT software, a reconstructed topographical image allows visualization of structures in a cross-sectional image providing new details of overall anatomic structures in different layers.[19] Since ICGA is not always available, and OCT is much more commonly used, we evaluated the ability of en face SD-OCT to image the characteristic findings of PCV seen on ICGA and to determine the relative size and extent of the lesion compared to ICGA.

METHODS

A retrospective, consecutive case series was conducted from January 2010 to November 2014 including 100 eyes of 84 patients with a diagnosis of PCV on ICGA from the clinics of Retina Consultants of Hawaii and The Retina Center at Pali Momi in Aiea, Hawaii. The Western Intuitional Review Board exempted this study from institutional review board approval because of its retrospective design (1-861556-1). This study adheres to the poli-

cies set forth by the Health Insurance Portability and Accountability Act and the Declaration of Helsinki.

The patients all received a baseline ophthalmic exam, fundus photos, fluorescein angiography (FA), and ICGA. The polypoidal complex was defined on ICGA as a nodular hyperfluorescent lesion or polyp often with a hypofluorescent halo with or without a BVN. ICGA and FA were performed using the Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany). All ICGA images were evaluated by one reading physician (GTK), who has extensive experience with PCV imaging[2,4,20] including studying with colleagues throughout Asia, where PCV is more common, and learning the ICGA diagnostic reading techniques utilized by the EVEREST multicentered PCV trial reading center in Singapore.[8]

En face SD-OCT images were performed with the Cirrus HD-OCT machine (Carl Zeiss Meditec, Dublin, CA), which uses the following for image acquisition: 512 A-scans per B-scan, 128 B-scans per volume, 1,024 pixels per A-scan on the 512 × 128 scans. The Cirrus En Face Report allowed for analysis and review of images. Multiple slabs and slab thicknesses were evaluated, but maximal visualization of the PCV complex was obtained with scans directed below the retinal pigment epithelium and above Bruch's membrane with a slab thickness varying from 25 microns to 33 microns. The RPE mode on en face imaging software allowed the en face image to follow the contour of the RPE, even if there was associated RPED.

A side-by-side comparison of ICGA images to en face OCT images was made by a single reviewer (GTK) to determine which modality was superior in identifying and diagnosing features of the PCV complex as well as delineating PCV lesion extent.

Data collected included demographic characteristics, ophthalmic exam findings, ophthalmic history, and previous treatment including prior anti-VEGF therapy and PDT. Baseline ICGA was evaluated for: 1) the ability to diagnose PCV by the characteristic PCV configuration — a subretinal vascular complex with polypoidal dilations with or without a BVN, and 2) the size and extent of the PCV lesion. The ability to make the diagnosis of PCV based on the characteristic findings and the full extent of the PCV complex were then evaluated and compared utilizing ICGA and en face SD-OCT scans in a side-to-side direct comparison.

RESULTS

Polypoidal choroidal vasculopathy was diagnosed by ophthalmic exam and ICGA in 100 eyes of 84 patients. Baseline demographic data and disease characteristics can be found in Table 1. The study included 62 treatment-naïve eyes (62%), 22 eyes (22%) treated with prior anti-VEGF therapy, and 16 eyes (16%) treated with prior photodynamic therapy (PDT). On en face OCT images, PCV was visualized as a dilated, irregular subretinal vascular structure with hyperreflective borders and polypoidal vascular dilations following the location and pattern initially visualized on ICGA.

TABLE 1
Patient Demographics and Baseline Disease Characteristics

Characteristic	Value
Number of Patients	84
Number of Eyes	100
Mean Age (Range)	76 (45-93)
Sex (Percentage)	
Female	37 (44%)
Male	47 (56%)
Ethnicity (Percentage)	
Asian	64 (76%)
White	15 (18%)
Other	5 (6%)
PCV Complex (Percentage)	
Laterality	
Unilateral	66 (79%)
Bilateral	18 (21%)
Location (Eyes, Percentage)	
Peripapillary	9 (9%)
Macular	85 (85%)
Both	6 (6%)

PCV = polypoidal choroidal vasculopathy

The PCV complex was better identified with en face SD-OCT in 44 eyes (44%) (Figure 1), ICGA in 45 eyes (45%) (Figure 2), and equally well in 11 eyes (11%). The techniques appeared complementary to each other, as the PCV complex was sometimes better visualized on ICGA, and other times was better visualized on en face SD-OCT. However, the ability to make the diagnosis of PCV by en face SD-OCT was supported in this preliminary study, and further studies are indicated to better define the role of en face SD-OCT.

The extent of the PCV complex borders (lesion size) was larger on en face OCT imaging in 65 eyes (65%), ICGA in 23 eyes (23%), and equal in size

TABLE 2

Visualization of PCV Based on Treatment Modalities

PCV Complex Identification (number, percentage)	Treatment-Naïve (62 eyes)	Anti-VEGF (22 eyes)	PDT (16 eyes)	Overall (100 eyes)
En face OCT > ICGA	24 eyes (39%)	11 eyes (50%)	9 eyes (56%)	44 eyes (44%)
ICGA > En face OCT	30 eyes (48%)	9 eyes (41%)	6 eyes (38%)	45 eyes (45%)
En face = OCT	8 eyes (13%)	2 eyes (9%)	1 eye (6%)	11 eyes (11%)
Extent of PCV Lesion				
En face OCT > ICGA	37 eyes (60%)	17 eyes (77%)	11 eyes (67%)	65 eyes (65%)
ICGA > En face OCT	16 eyes (26%)	3 eyes (14%)	4 eyes (25%)	23 eyes (23%)
En face = OCT	9 eyes (15%)	2 eyes (9%)	1 eye (6%)	12 eyes (12%)

ICGA = indocyanine green angiography; OCT = optical coherence tomography; PCV = polypoidal choroidal vasculopathy; VEGF = vascular endothelial growth factor

on both imaging modalities in 12 eyes (12%). The results of the visualization and extent of the PCV complex based on treatment modality are in Table 2.

On baseline exam, 20 eyes (20%) had a RPED present. The RPED makes visualization of the PCV complex difficult on both ICGA and on en face OCT. On ICGA utilizing the scanning laser ophthalmoscope, there was a dark hypofluorescent area corresponding to the RPED, which blocked visualization of any details of the PCV complex (Figure 3). On en face OCT, there was a hyporeflective area with poor visualization of details (Figure 3). However, the PCV complex can be visualized in the notch of the RPED or extending adjacent to the RPED. Visualization of the PCV complex in eyes with RPED was better on ICG in 10 eyes (50%), better on en face SD-OCT in nine eyes (45%), and equally visualized in 1 eye (5%). However, the extent of the PCV complex was larger on en face SD-OCT in 17 eyes (85%) and on ICGA in three eyes (15%)(Figure 3).

DISCUSSION

En face SD-OCT was able to visualize the typical features of the PCV complex thus providing a means to image and make the diagnosis of PCV utilizing a non-invasive and widely available technology. In fact, in 55% of the PCV cases in this study, en face SD-OCT was as good as or better than ICGA in imaging the characteristic features of PCV. In the treatment-naïve patients ICGA better visualized the PCV complexes than the en face SD-OCT. In patients that were previously treated with PDT or anti-VEGF therapy en face SD-OCT was slightly better than ICGA in PCV complex identification. However, en face SD-OCT imaging does not replace ICGA, as 45% of the total cases showed a much more characteristic feature on ICGA then en face OCT (Figure 2). In a smaller study from Japan utilizing en face OCT imaging with a swept-source OCT (OCT-ophthalmoscope C7; Nidek, Fremont, CA), en face OCT also confirmed the diagnosis of PCV in eyes previously diagnosed with ICGA, correctly identifying 84.2% of polypoidal lesions as small round protrusions and 52.6% of the BVN as smaller elevations of the RPE.[21] The Japanese study did not compare the ability to make the diagnosis of PCV overall between ICGA and en face OCT but also confirmed the utility of en face OCT in imaging PCV.

In PCV eyes with a RPED evaluated by Saito et al., en face images showed small protrusions with highly reflective rings in which all lesions corresponded to polypoidal complexes on ICGA.[22] In eyes with a RPED in this study, en face SD-OCT equally or better identified the PCV complex in half the eyes with a RPED. Furthermore, en face SD-OCT better visualized the extent of the PCV complex borders in 85% of eyes with a RPED.[22] As mentioned before, the RPED can often block visualization of the PCV complex on ICGA with scanning laser ophthalmoscope. Further studies may further evaluate this potential advantage of en face OCT in imaging PCV complexes with an associated RPED, which is a common clinical presentation in eyes with PCV.

Overall in this study, the extent of the PCV complex was larger in 65% of study eyes on en face SD-OCT than on ICGA regardless of treatment status (Table 2). We speculate that this is because en face SD-OCT images the PCV complex with the surrounding extravascular matrix and RPE draped over the type I subretinal neovascular complex that

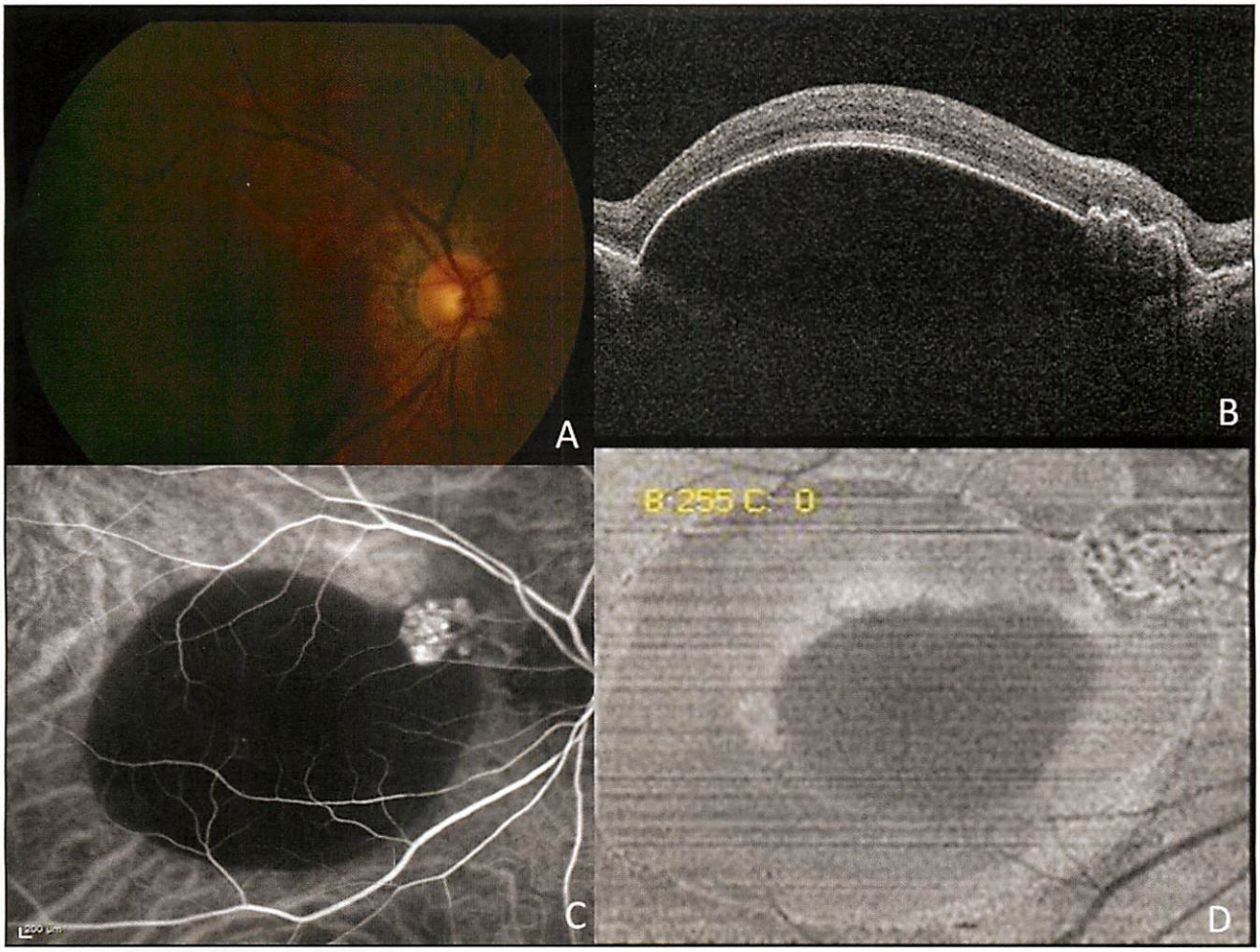

Figure 3. The polypoidal complex was better visualized on en face optical coherence tomography (OCT) than the corresponding indocyanine green angiography (ICGA) in this patient who has a large retinal pigment epithelium detachment (RPED). (A) Fundus photo of the right eye in an Asian male with previous bevacizumab therapy. (B) OCT line scan shows a large RPED with nasal polyps. (C) ICGA displaying supernasal polypoidal choroidal vasculopathy (PCV) complex with large RPED corresponding to the hypofluorescent lesion within the macula. (D) En face OCT showing better visualization of the nasal PCV complex.

is under the RPE, whereas ICGA images blood flow through the lumen of the subretinal neovascularization without imaging the overlying RPE. Secondly, in eyes that were previously treated, there may be polypoidal vascular structures that persist but lack blood flow after treatment and are thus not visualized on ICGA, but are still imaged on en face SD-OCT.

Sayanagi et al. reported en face enhanced depth imaging SD-OCT (EDI SD-OCT, Topcon, Tokyo, Japan) with swept-source technology and found en face OCT identified 95% of polypoidal complexes.[23] Swept- source imaging provides a theoretical advantage over other spectral-domain en face technologies by providing enhanced depth and imaging of the choroid. Furthermore, they noted that six eyes had polypoidal lesions on EDI SD-OCT that were not observed on ICGA. Similar to what we discussed above, the authors proposed that a lack of blood flow through the PCV lesion was the etiology of this finding given the high number of treated patients in their patient series.[23,24]

This study highlights the importance and utility of en face OCT in imaging PCV. Although B-scans can give horizontal cross sectional images of pathology, en face OCT offers an advantage by producing a topographic image that leads to visualization and enhanced recognition of the entire PCV complex. This is especially beneficial in patients with a poor response to anti-angiogenic therapy who may require PDT therapy. Especially in treatment-naïve eyes, the en face OCT image could potentially guide the PDT therapy while also providing an overall diagnosis of the characteristic polyps

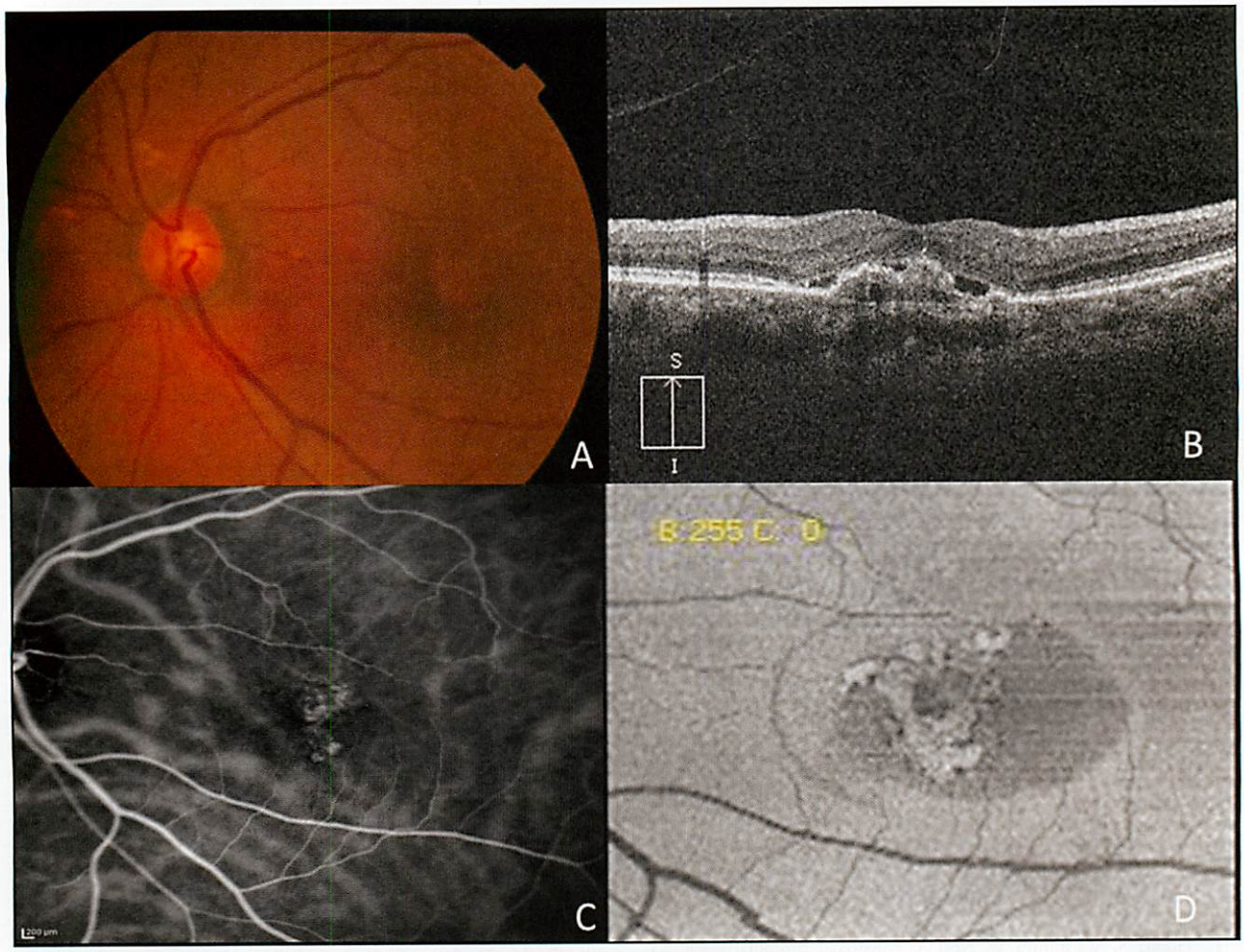

Figure 4. The polypoidal complex was better visualized on en face optical coherence tomography (OCT) than the corresponding indocyanine green angiography (ICGA) in this patient, who was previously treated with photodynamic therapy and anti-vascular endothelial growth factor therapy. (A) Fundus photo of the left eye in an Asian female. (B) OCT line scan shows a type I choroidal neovascular membrane with subretinal fluid. (C) ICGA displaying the branching vascular network, with incomplete visualization of the complex. (D) En face OCT showing a dilated vascular structure with complete visualization of the polypoidal choroidal vasculopathy complex.

and BVN leading to the diagnosis of PCV that has previously been conventionally made with ICGA. However, in this qualitative observational study, it was noted that in eyes with PCV previously treated with PDT, the en face SD-OCT images visualized a larger extent of the lesion borders (Figure 4). As discussed, this may indicate that the en face OCT images both perfused and nonperfused parts of the PCV complex, which may make the en face SD-OCT less useful for PDT treatment guidance in eyes already having prior treatment.

The limitations of this study include its retrospective design and the inclusion of eyes that were previously treated. In previously treated eyes, ICGA may show decreased flow and decreased polyps, whereas the en face OCT demonstrates the full vascular complex of PCV with or without perfusion. The analysis of ICGA and en face SD-OCT was qualitative, and done in a side-by-side comparison of the two imaging methods. Future quantitative parameters such as measuring PCV complex size, and specific polyp numbers can be considered in future studies. Another limitation is the use of a single experienced examiner, but there are currently few good guidelines on ICGA interpretation, and very few experienced diagnostic examiners of ICGA for PCV. In addition, this was an exploratory study of a new technology — en face SD-OCT — to assess its ability to image structures diagnostic of PCV compared to ICGA, and, since it was positive, to stimulate further research of this technology and more widespread use of this imaging modality to make the diagnosis of PCV. Further study is necessary to determine if this can be utilized by multiple

examiners and practitioners, even in areas where PCV may not be as common.

In conclusion, en face SD-OCT visualizes PCV as a subretinal vascular structure with hyperreflective borders and polypoidal dilations with or without a branching vascular network, which follows the pattern of the PCV complex identified by ICGA. As previously shown with B-scan OCT images,[2] en face OCT confirms the location of the PCV complex below the retinal pigment epithelium and above Bruch's membrane (type I CNV). ICGA and en face SD-OCT were complementary in the diagnosis of PCV with each technique better imaging the PCV complex in some patients. En face OCT does image a larger extent and size of PCV complexes in patients who have a RPED present and in treated and treatment-naïve patients. En face OCT is a widely available, fast, and noninvasive imaging modality, which with increased clinical usage could play an important role in helping to identify eyes with serosanguinous maculopathy, who have a PCV complex. This is especially important in eyes relatively resistant to intravitreal antiangiogenic drugs, and when ICGA may not be available.

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