

Detection of choroidal neovascularisation in flat irregular pigment epithelial detachment in central serous chorioretinopathy using optical coherence tomography angiography: en-face image combined with cross-sectional image

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Abstract

Background: This study investigated choroidal neovascularisation (CNV) in FIPED by two methods: en-face OCTA and cross-sectional OCTA. We intended to evaluate the incidence of CNV and compare the efficacy of each imaging modalities.

Methods: We retrospectively studied OCT and OCTA images of 328 eyes with CSC. OCTA B-scans and macular cube scans were primarily reviewed for the detection of FIPED and CNV. En-face OCTA and cross-sectional OCTA with Angio-B view, which is an image that combines an OCT B-scan with a flow signal were analysed to evaluate the presence of CNV in FIPED.

Results: Among 93 eyes of 88 patients with FIPED, CNV was observed in 23 eyes on en-face OCTA and 21 eyes on cross-sectional OCTA. There were eight discrepant cases, in which the findings were not consistent with that of cross sectional OCTA.

Conclusions: The CNV and FIPED lesions were well detected on both cross-sectional and en-face OCTA. Integration of these two imaging modalities can further improve the efficacy of OCTA in differentiating CNV from FIPED lesion.

Background

Central serous chorioretinopathy (CSC) is characterised by serous detachment of the neurosensory retina and is associated with retinal pigment epithelium (RPE) alteration. It is diagnosed predominantly in young or middle-aged individuals [1, 2].

In fluorescein angiography (FA), diffuse RPE defects can be visualised and a single point or multifocal leakage points are observed according to the degree of chronicity. Indocyanine green angiography (ICGA) shows dilation of large choroidal veins in the mid-phase. Choroidal vascular hyperpermeability and congestion are thought to be the main causes of CSC development [3]. Optical coherence tomography (OCT) can identify various aspects of RPE alterations, according to the CSC chronicity [4].

Flat irregular pigment epithelium detachment (FIPED) is one of the pigment epithelial detachment (PED) patterns of CSC. It is mainly observed in chronic CSC compared with acute CSC. It has an irregular RPE elevation compared to a dome-shaped PED. Most FIPEDs are known to be avascular, however, choroidal neovascularisation (CNV) in FIPED has been reported in long-standing CSC cases [5, 6]. Because of multiple RPE changes and dilated pachy-vessels of the choroid, it is often difficult to identify CNV on FA or ICGA [7].

Optical coherence tomography angiography (OCTA) is a new imaging modality that can detect blood flow without invasive dye injection. Recent publications reported that it can effectively identify the presence of CNV in FIPED as an en-face image [8-10].

However, the analysis using an en-face image in the existing OCTA protocol may result in errors, such as motion artefacts, projection artefacts, layer segmentation errors, and flow signal masking that can occur during the calibration of projection artefacts. En-face imaging is challenging because the size of FIPED is very small to be accurately divided and analysed in layers. Manually correcting the layer segmentation for each cross-sectional image may be feasible only for research purposes; however, it is not quite accurate to rely on automated computer analysis. To overcome these limitations, cross-sectional OCTA was introduced for clinical application. Cross-sectional OCTA provides flow signal with false colour code overlaid on OCT B-scan. It is possible to readily observe the flow signal in the PED, with less confusion caused by artefacts produced in the process of creating the en-face image. This study investigated CNV in FIPED by two methods: en-face OCTA and cross-sectional OCTA. We intended to evaluate the incidence of CNV and compare the efficacy of each imaging modalities.

Methods

Study design and ethical statement

We retrospectively reviewed the medical records of 290 patients (328 eyes) with acute and chronic CSC who visited the Department of Ophthalmology at Hanyang University Hospital between February 1, 2016, and February 1, 2018. This study was conducted according to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board at Hanyang University Seoul Hospital.

Eyes with other retinal abnormalities, such as polypoidal choroidal vasculopathy, age-related macular degeneration, idiopathic choroidal neovascularisation or other retinal vascular diseases, intraocular inflammation, and posterior segmental tumour were excluded. In addition, we excluded patients who had steroid-induced CSC and organ transplant-associated CSC. According to the manufacturer's recommendation [11], images of poor quality (image quality score lower than 45) provided by the onboard OCT software were excluded.

Definitions

The definitions used in this study were adapted from previous reports [2]. CSC was defined as a retinal disease characterised by serous detachment of the neurosensory retina secondary to one or more focal lesions of RPE [12]. Chronic CSC was defined as presence of symptoms for more than six months, history of recurrence, background fundus change, such as atrophic retinal and RPE changes, visible drainage tract or other atypical dye leakages during FA initial examination [4, 13]. Intravitreal anti-Vascular endothelial growth factor (VEGF) injection and photodynamic therapy (PDT) history were not excluded from the study criteria.

FIPED was defined as a small, flat, and irregular surface PED on the OCT B-scan. Unlike semi-circular PED, RPE elevation is not large but the RPE layer is separated from Bruch's membrane and a "double layer sign" is observed [14]. The sub-RPE space at the site of FIPED showed either hypo-reflection (not optically filled) or at least partial hyper-reflection, as previously described [7].

Study protocol

Patients' medical records were reviewed, including best-corrected visual acuity, spherical equivalent, dilated fundus biomicroscopy findings, and multimodal imaging data including OCT, FA, ICGA, and OCTA.

All subjects underwent OCT and OCTA with Swept-source optical coherence tomography (SS-OCT) (Deep range imaging OCT, Triton, Topcon, Tokyo, Japan). We identified the presence of FIPED on OCT B-scans (Topcon SS-OCT parameters: 100 KHz, A-scan rate, wavelength 1050 nm). This study used OCTA ratio analyses employed by Topcon, which is an intensity ratio analysis, not based on amplitude-decorrelation. A 3 x 3 mm volume scan was performed, and each B-scan's position was automatically scanned four times. All OCT and OCTA assessments were performed by two trained retinal specialists (B.R.L. and S.J.A.) who were not aware of each other's imaging findings. OCTA B-scans and the 3 x 3 mm OCTA macular cube scans were primarily reviewed for the detection of FIPED and the presence or absence of CNV at the site of the FIPED. If a 3 x 3 mm OCTA image did not show any FIPED, the findings were confirmed through evaluation of the 4.5 x 4.5 mm or 6 x 6 mm OCTA B-scans. FA and ICGA (F-10, Nidek, Tokyo, Japan) was also performed, and assessed by the two specialists (B.R.L. and S.J.A.).

Choroidal neovascularisation using en-face OCTA and cross-sectional OCTA

When FIPED was confirmed, the OCTA image was analysed to evaluate the presence of CNV in FIPED. Using OCTA software, the retinal layers and generated en-face images of the superficial plexus, deep plexus, avascular retina, and choriocapillaris were automatically segmented. The inner plexiform layer (IPL)/inner nuclear layer (INL) line and the Bruch's membrane (BM) line were created by automated segmentation. Next, the en-face image of the outer retina (from 70.2 μ m under IPL/INL line to BM line) and choriocapillaris (from BM line to 10.4 μ m under BM line) was constructed. For en-face OCTA, these two images were analysed to evaluate the presence of CNV in FIPED.

The OCT B-scans were then combined with the corresponding en-face OCTA images, and scrolling was enabled through the sections similar to that of OCT cube scan. In the cross-sectional OCTA, we used the Angio-B view provided by the Topcon, which is an image that combines an OCT B-scan with a flow signal coated with a false-colour code. The cross-sectional view helped identify the flow signal in the FIPED by providing scrolling function. It was possible to distinguish between projection artefacts and the real flow signals by checking the sequential sections.

As diagnosed in other studies [8, 10, 14, 15], CNV was confirmed with comprehensive data; clinical history and multimodal imaging data including OCT, FA, ICGA, and OCTA.

Results

Study population

This study retrospectively analysed the medical records of 290 patients (328 eyes), of which 256 patients (279 eyes) were actually included in the final analysis. In the remaining 15 patients (26 eyes), OCTA was

not performed or the image quality was found to be poor. Age-related macular degeneration (AMD) was suspected on FA and ICGA in seven patients (10 eyes). A total of 13 eyes (12 patients) with other retinal diseases were excluded. FIPED was detected in 93 eyes of 88 patients (approximately 33.3%). The mean age of patients was 55.34 ± 11.86 years, and 79.6% (74 eyes, 69 patients) had chronic CSC.

Choroidal neovascularisation in FIPED

CNV was observed in 23 eyes on en-face OCTA and 21 eyes on cross-sectional OCTA, among 93 eyes with FIPED. Actual CNV was diagnosed by clinical data and multimodal imaging was noted in 21 eyes. The specificity and sensitivity of CNV detection using en-face OCTA alone and in combination with cross-sectional OCTA are shown in Table 1. True and false positives, negatives are presented in Table 2. There was no significant difference in terms of age ($p > 0.05$; 59.41 ± 9.49 years for those with CNV, 51.29 ± 11.93 years for those without CNV). All 21 cases of CNV were detected in those with chronic CSC.

Table 1. Sensitivity and specificity of detection of choroidal neovascularisation

Imaging modality	Sensitivity/specificity
En-face OCTA alone	85.7% (18/21)
	93.1% (67/72)
En-face OCTA with cross-sectional OCTA	100% (21/21)
	100% (72/72)

OCTA - Optical coherence tomography angiography

Table 2. True and false positives, negatives in detection of choroidal neovascularisation

Imaging modality	True positives	False positives
	False negatives	True negatives
En-face OCTA alone	18	5
	3	67
En-face OCTA with cross-sectional OCTA	21	0
	0	72

OCTA - Optical coherence tomography angiography

Case descriptions

CNV in FIPED was observed in 21 eyes with cross-sectional OCTA and 23 eyes with en-face OCTA. 18 eyes showed CNV in both en-face and cross-sectional OCTA. There were eight discrepant cases, in which

CNV was observed on en-face OCTA, but not on cross-sectional OCTA. In the remaining cases, however, cross-sectional OCTA, but not en-face OCTA, could detect CNV. Figure 1-3 introduce several cases of correspondence and discrepancy.

No discrepancy in en-face OCTA and cross-sectional OCTA

Figure 1 shows OCTA images of four cases among 18 eyes in which there was no discrepancy in the results of en-face and cross-sectional OCTA. Figure 1-(A), (B), (C), and (D) are the 3 x 3 mm sections of en-face OCTA and Figure 1-(E), (F), (G), and (H) are the corresponding cross-sectional OCTA images. Both en-face OCTA and cross-sectional OCTA could detect CNV in FIPED. Figure 2 and 3 show cases of discrepancy between the two methods.

Discrepancy in en-face OCTA and cross-sectional OCTA

Figure 2 shows two cases of CNV in the en-face view [in (A) and (B)], however, absence of CNV was confirmed by cross-sectional OCTA [in (C) and (D)] with projection artefacts. Among a total of 5 cases (5.38%), 4 cases were identified as projection artefacts and 1 due to a segmentation error because of the choriocapillaris layer appearing under the FIPED. Figure 3 shows discrepancy of the CNV on en-face OCTA in 3 eyes (3.23%). A clear flow signal was observed in the cross-sectional OCTA; however, PED size was small, and it was masked in the process of removing projection artefacts in the en-face OCTA. Thus, among the 93 eyes, 21 cases of CNV in FIPED were identified and 8 cases showed discrepant results.

Discussion

In this study, of the 93 eyes with FIPED, CNV was observed in 21 eyes. The prevalence of CNV was 22.6%, which was closer to the lower border reported in previous studies. Previous reports have confirmed the presence of CNV in 18.9-58% of chronic CSC cases [7, 10, 14].

Using OCTA, several studies have quantified vessel density and flow index [16], as well as CNV [17, 18]. Accurate segmentation is important to interpret and quantify OCTA findings. However, in eyes with retinal pathology such as chronic CSC, the margins of the retinal layer are distorted and precise boundary segmentation can be difficult. Although many researchers have attempted to improve the quality of automated segmentation in diseased eyes [19, 20], accurate automated segmentation is not achieved in all clinical cases. Therefore, manual correction of segmentation is often required [21, 22]. In cases of chronic CSC, most FIPEDs are known to be avascular, although CNV in FIPED has been reported [5, 6]. However, because of multiple RPE changes and dilated pachy-vessels of the choroid, it is often difficult to detect CNV on FAG or ICGA [7].

Recently, several studies on PED using en-face views in OCTA have been performed [8, 10, 14, 15]. However, analysis using en-face images may result in errors, such as motion artefacts, projection artefacts, layer segmentation errors, and flow signal masking that can occur during the calibration of projection artefacts. To complement this, cross-sectional OCTA, obtained by adding the flow signal to the

existing OCT B-scan with false colour code, was introduced. It is possible to observe the flow signal in the PED without being affected by the errors that may occur in creating the en-face image. This results in continuous sectional views on scrolling. In cases of PCV and PED in AMD, some studies using cross-sectional OCTA as well as en-face view have been published [23-26].

It is important that the entire morphology of a CNV lesion is thoroughly analysed to qualitatively define a choroidal neovascular network, based on the shape, branching, anastomoses, type of vessels termini, and presence of hypointense perilesional halo [27]. However, there could be some errors in en-face OCTA due to the abovementioned difficulties. Since CNV is not a coplanar structure, it may show a different morphology at each level of depth. En-face OCTA provides depth-resolved images; therefore, manual confirmation of the cross-sectional B-scan allows a layer-by-layer tomographic visualisation of the entire neovascular feature.

This study is significant because of the identification of CNV on FIPED of chronic CSC using both en-face and cross-sectional OCTA. The CNV in FIPED was observed in 23 eyes on en-face OCTA and 21 eyes on cross-sectional OCTA. The diagnostic efficacy of both the methods was similar; however, eight cases showed discrepant results on en-face OCTA. Among them, five were false-positive cases, i.e., en-face OCTA detected the presence of CNV but there was no actual CNV in these eyes (Figure 2). Four cases were identified as projection artefacts and one case as a segmentation error with the choriocapillaris layer under FIPED. The remaining 3 eyes had confirmed CNV, but no CNV was seen on en-face OCTA. The reason for the false negativity was the small size of PED that could not be detected on en-face OCTA and masked PED in the process of removing projection artefacts. A total of eight eyes showed discrepant results on en-face OCTA that could not be ignored, and cross-sectional OCTA was required to compensate for these errors. With cross-sectional OCTA, a more complete layer-by-layer analysis of the entire structure could be performed to detect the precise location of the CNV lesion relative to the RPE layer.

When FIPED is observed in chronic CSC, it is not necessary to consider anti-VEGF treatment for the possibility of type 1 CNV. In this study, CNV in FIPED was found in 21 out of 93 eyes, and less than one-third of cases of active CNV. Previous studies have reported that OCTA findings in PED were caused by the severe choriocapillaris alteration in those with AMD [18, 28]. However, the vascular signal in FIPED with chronic CSC seems to be due to compensatory choriocapillaris vascular remodelling owing to a weak Bruch's membrane. The CNV lesion described as a "darker halo" or total absence of choriocapillaris with loss of both the inner and deeper choroidal vessels encircling the CNV lesions could not be found in this study. Therefore, careful observation in these cases compared to AMD is recommended.

This study included both acute and chronic CSC and there were many subjects with SRF. The presence of SRF might affect en-face OCTA image analysis because it is a major change of retinal layers which could cause many artefacts. But in the present study, we could not find any relationship between them. Further study regarding the differences in detection rate associated with SRF would be beneficial.

Limitations of this study are the retrospective design and relatively small sample size. Additionally, this study investigated the strength of cross-sectional views, and unlike for the en-face view, clinicians need to

observe each CNV lesion using manual scrolling. In addition, longitudinal studies are needed to confirm changes in CNV lesions in FIPED in chronic CSC patients. However, this study has value in that it is the first study to analyse CNV in FIPED in chronic CSC patients using both en-face and cross-sectional OCTA.

Conclusion

In conclusion, this study demonstrates the potential feasibility of using cross-sectional OCTA to detect CNV. To identify CNV in FIPED without dye angiography, the reliability of detecting flow signal within any pathological lesion is critical. The clinical use of cross-sectional OCTA, as well as en-face OCTA to interpret FIPEDs may help clinicians in decision-making. Integration of these two methods can potentially improve the utility and diagnostic accuracy of OCTA.

Abbreviations

CSC: Central serous chorioretinopathy; RPE: Retinal pigment epithelium; FA: Fluorescein angiography; ICGA: Indocyanine green angiography; OCT: Optical coherence tomography; FIPED; Flat irregular pigment epithelium detachment; PED: Pigment epithelial detachment; CNV: Choroidal neovascularisation; OCTA: Optical coherence tomography angiography; VEGF: Vascular endothelial growth factor; PDT: Photodynamic therapy; SS-OCT: Swept-source optical coherence tomography; IPL: Inner plexiform layer; INL: Inner nuclear layer; BM: Basement membrane; AMD: Age-related macular degeneration

Declarations

Ethics approval and consent to participate

This study adhered to the tenets of the Declaration of Helsinki. This study was approved by our Institutional Review Board.

Consent to publish

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SJR and JSL contributed equally to this work.

Conception and design: SJR, SHL, SJA, and BRL; Data collection: SJR, SHL, SJA, and BRL; Analysis and interpretation: SJR, SHL, SJA, and BRL; Writing the article: SJR, JSL, SHL, SJA, and BRL; Critical revision of the article: SJR, JSL, SHL, SJA, and BRL; Final approval of the article: SJR, SHL, SJA, BRL. All authors have read and approved the manuscript.

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Figures

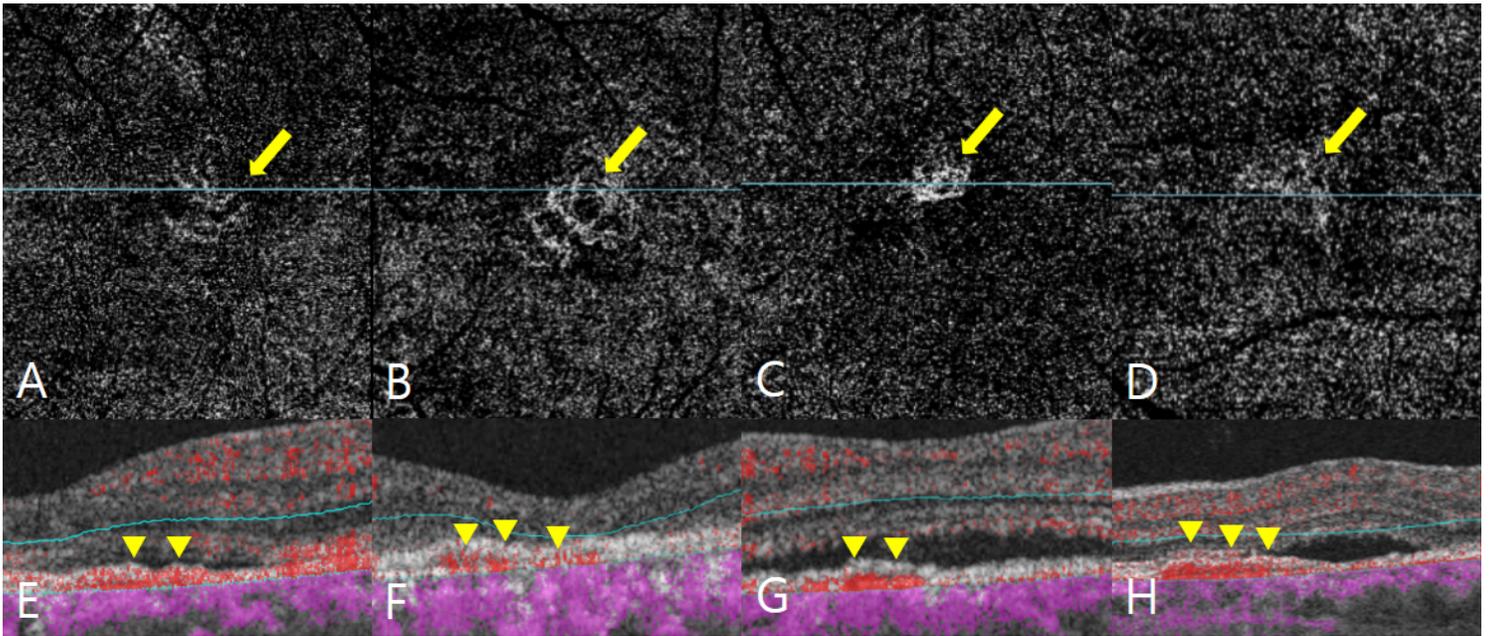


Figure 1

Representative cases of correspondence between the en-face view and the cross-sectional view. (A)-(D) The 3 × 3 mm en-face view shows Choroidal neovascularisation (CNV) (arrows). Horizontal line is the line of cross-sectional view. (E)-(H) In the same lesions, cross-sectional views show the flow signal (arrow heads) in Flat irregular pigment epithelium detachment (FIPED). Both en-face view and cross-sectional view show CNV in FIPED.

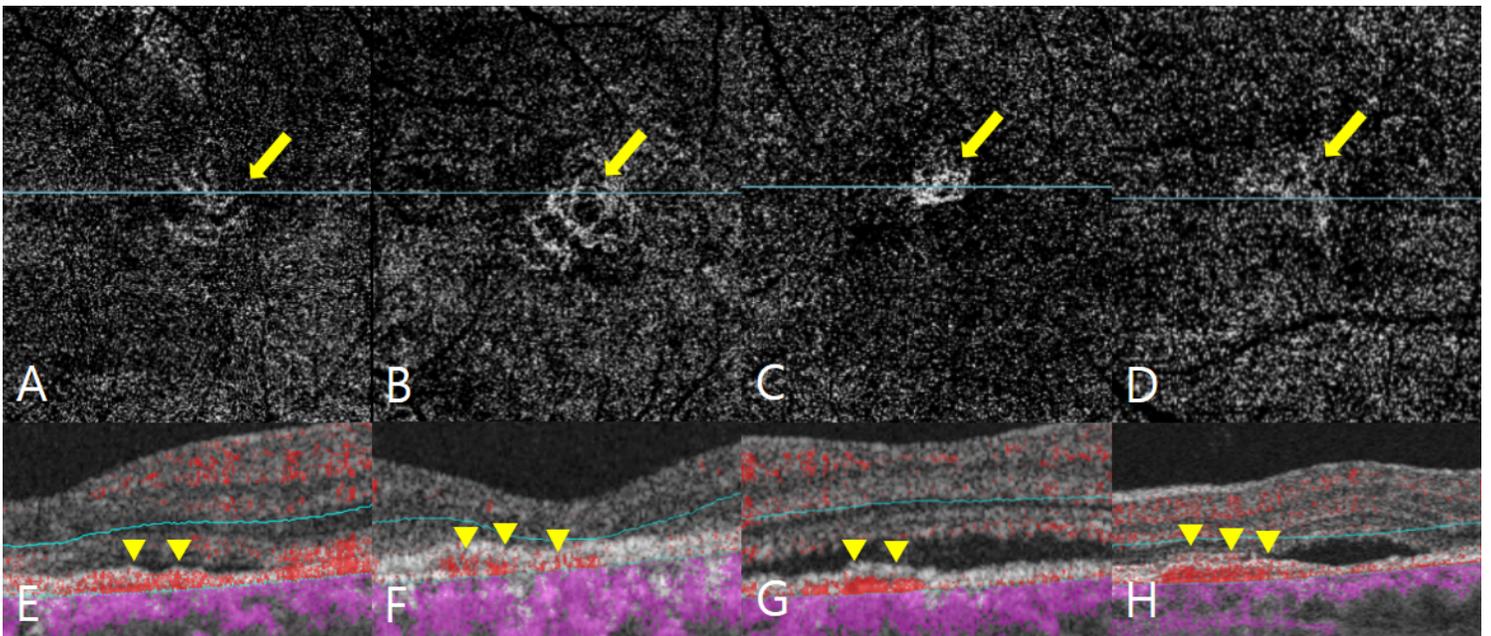


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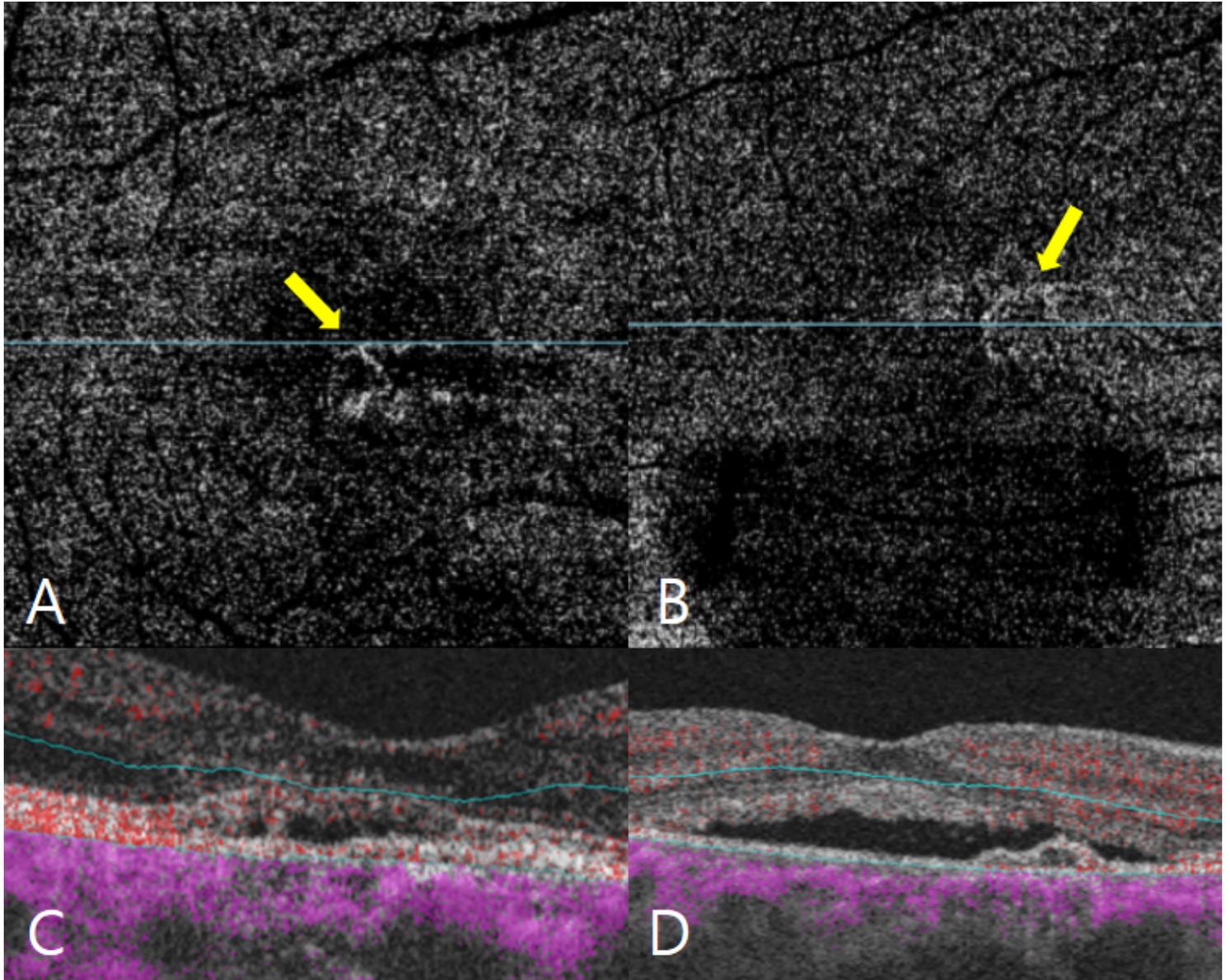


Figure 2

Representative cases of discrepancy between the en-face view and the cross-sectional view. Upper figures of the en-face view represent CNV (arrows) (A, B). Horizontal line is the line of cross-sectional view. There is no positive flow signal in the corresponding lesions in the cross-sectional views (C, D). There is no CNV in the pigment epithelial detachment when assessed by cross-sectional view in 5 cases (5.38%). Among them, four cases were identified as projection artefacts and one case as a segmentation error due to the choriocapillary layer under FIPED.

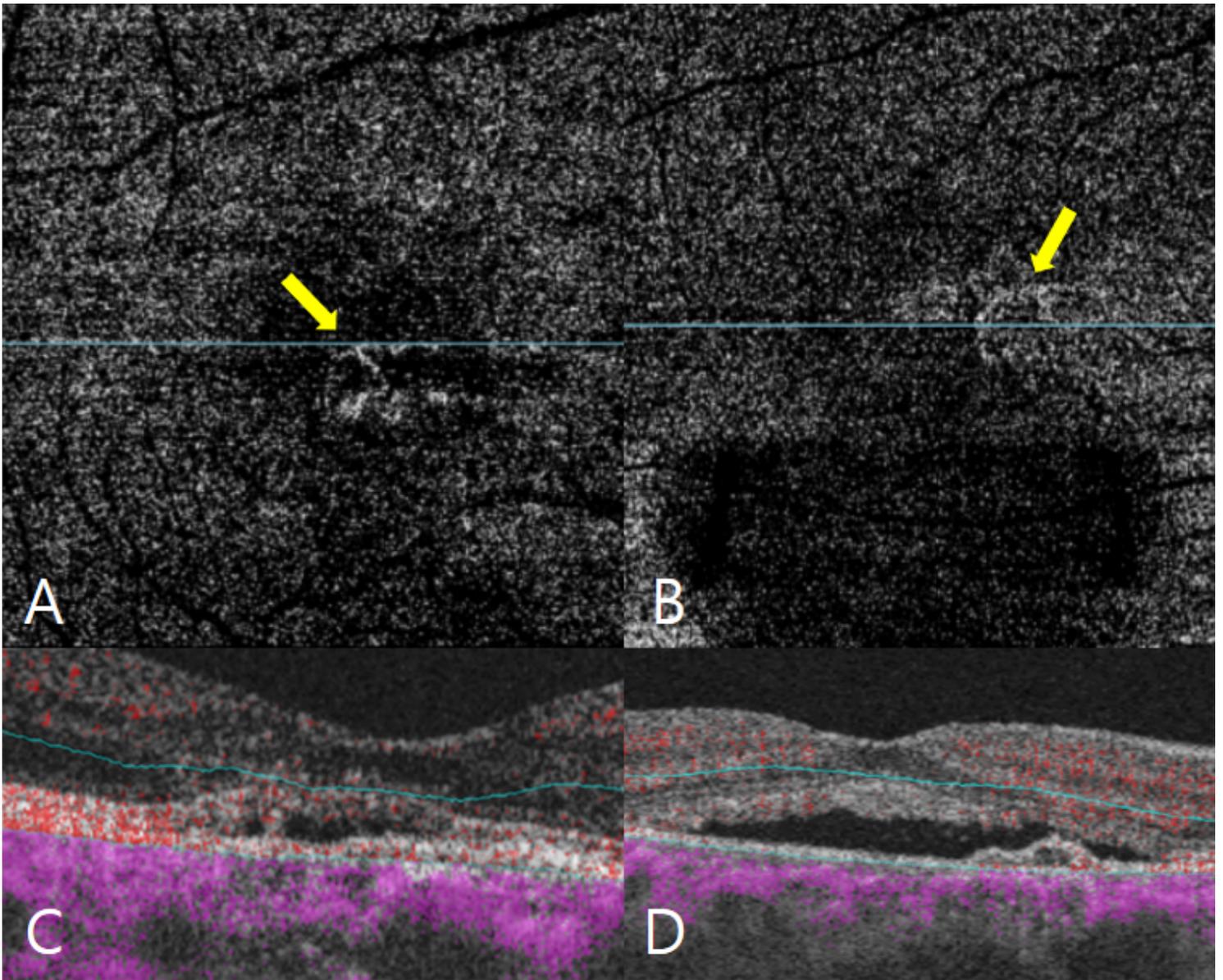


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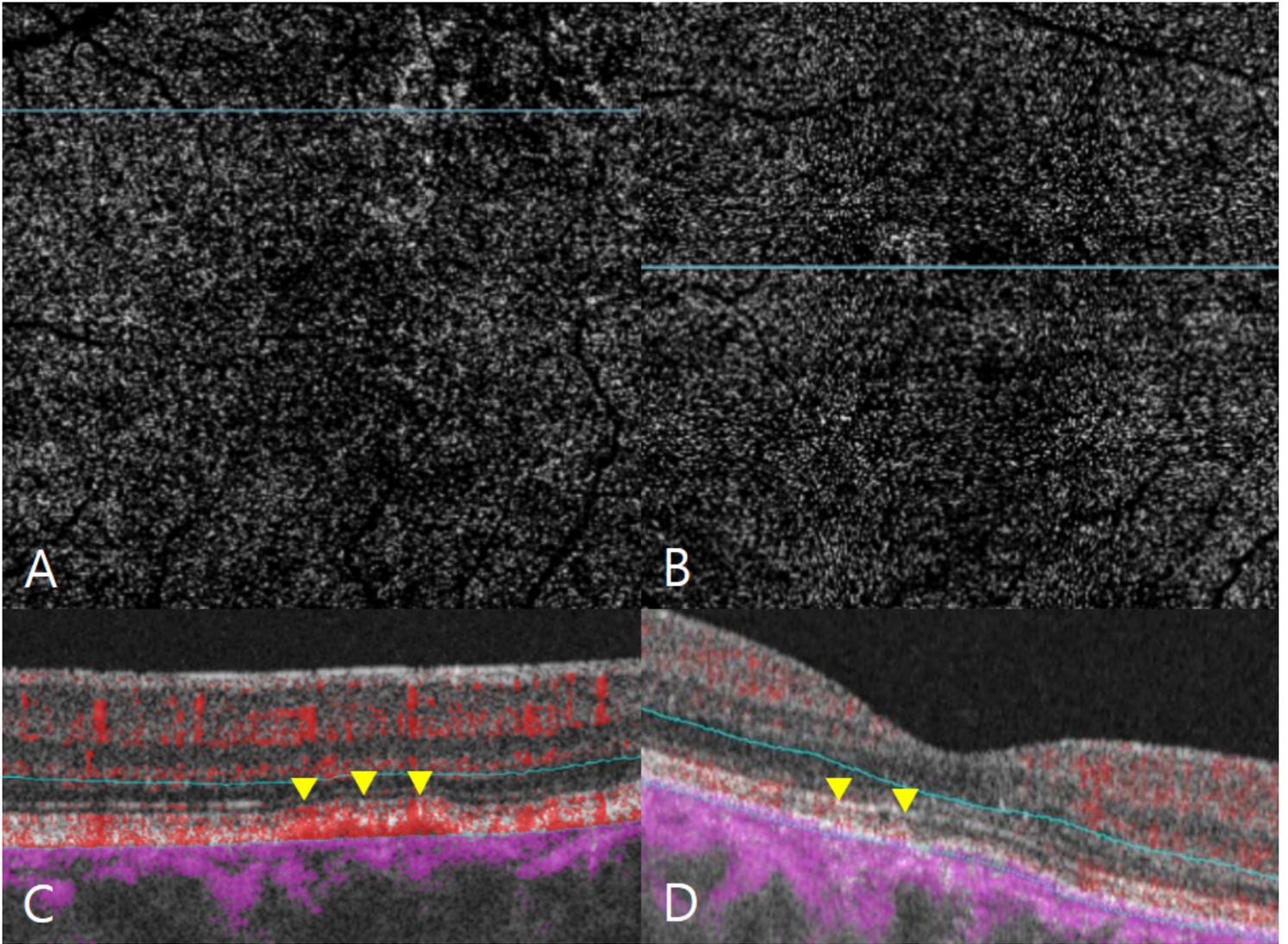


Figure 3

Representative cases of discrepancy contrary to Figure 2. The en-face views (A and B) do not show any CNV. Horizontal line is the line of cross-sectional view. Positive flow signal can be observed in the cross-sectional OCTA (C and D), but PED size appears very small, and it is masked in the process of removing projection artefacts in the en-face Optical coherence tomography angiography (OCTA).

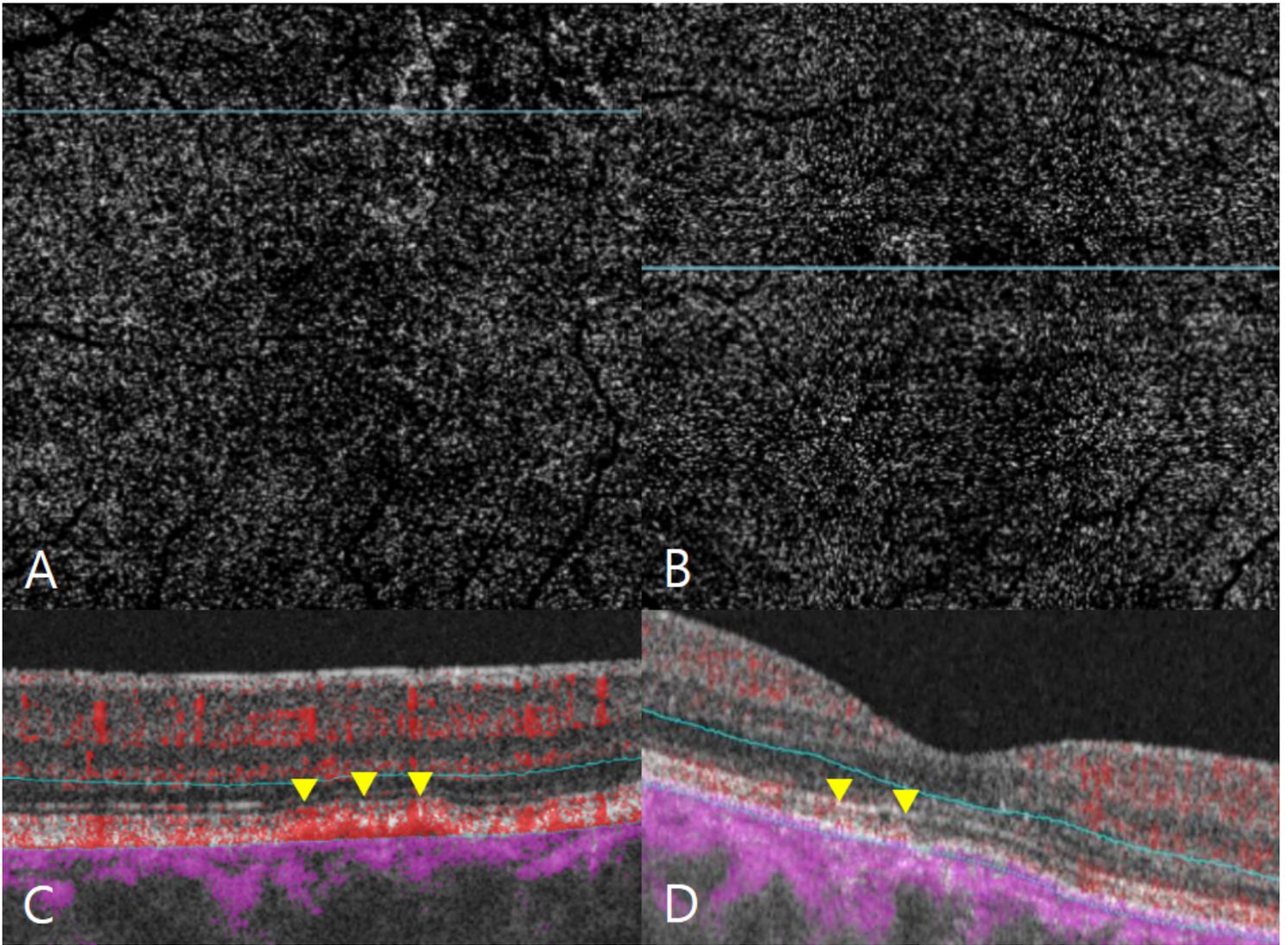


Figure 3

Representative cases of discrepancy contrary to Figure 2. The en-face views (A and B) do not show any CNV. Horizontal line is the line of cross-sectional view. Positive flow signal can be observed in the cross-sectional OCTA (C and D), but PED size appears very small, and it is masked in the process of removing projection artefacts in the en-face Optical coherence tomography angiography (OCTA).