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Case report

Changes in choroidal blood flow velocity in patients diagnosed with central serous chorioretinopathy during follow-up for pachychoroid pigment epitheliopathy

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ABSTRACT

Purpose: To evaluate chronological changes in choroidal blood flow velocity in two patients with pachychoroid pigment epitheliopathy (PPE) and central serous chorioretinopathy (CSC) in the same eye.

Observations: Two males aged 36 and 43 years old with PPE were diagnosed with CSC in the same eyes during follow-up. Using laser speckle flowgraphy, the macular mean blur rate (MBR), an index of relative blood flow velocity, was sequentially evaluated in the affected and unaffected eyes. In the affected eye, the macular MBR values at the onset of PPE and CSC were higher, at 25% and 33% in Case 1 and 21% and 51% in Case 2, respectively, than those on PPE regression; but the same trends were not observed in their fellow eyes. The increases in MBR changing rates were 1.3 and 2.5 times higher in Cases 1 and 2, respectively, at the onset of CSC than those at the onset of PPE.

Conclusion and importance: In the affected eyes, the rates of MBR change increased at the alternate onsets of PPE and CSC. The increased MBR changing rates were 1.3–2.5 times higher at the onset of CSC than those at the onset of PPE. Our data suggest that choroidal hyperperfusion is involved in the pathogenesis of both diseases and that its severity may differ between CSC and PPE. These results may support the hypothesis that PPE and CSC clinically overlap and have a common pathogenic background.

1. Introduction

Pachychoroid pigment epitheliopathy (PPE), a pachychoroid spectrum disorder,[1] is a retinal pigment epitheliopathy with similar clinical features to central serous chorioretinopathy (CSC), but without serous retinal detachment (SRD).[1,2] Clinical findings common to PPE and CSC include dilated choroidal veins and choroidal hyperpermeability (CVH) on indocyanine green angiography (ICGA), and an increase of the choroidal thickness and pachyvessels on optical coherence tomography (OCT).[3] Macular morphological features on OCT show loss of the ellipsoid zone/interdigitation zone, dome-shaped hyper-reflectivity at the retinal pigment epithelium (RPE), or small pigment epithelial detachment (PED) above pachyvessels, corresponding to the PPE lesions.[1–5]

In patients with unilateral CSC, 61% were reported to suffer from PPE in their fellow eye,[6] although this may include impairment of the RPE following regression of CSC in the fellow eye due to the cross-sectional study design. Longitudinal investigations of the clinical course in patients with PPE have reported only approximately 10 cases.[2,5] Of these patients, only one developed CSC during follow-up.[5] Therefore, the relationship between PPE and CSC remains unresolved, although it is hypothesized that there is a relationship between the two diseases in terms of their pathogenesis.[1]

Laser speckle flowgraphy (LSFG) has been used to investigate choroidal blood flow velocity.[7] LSFG has the advantage of allowing quantitative and repeated measurements of choroidal circulation to evaluate the time course of diseases[8–11] and diurnal changes in healthy subjects.[12] Using LSFG, the mean blur rate (MBR), a relative index of blood flow velocity, at the macula was shown to significantly increase at the acute stage of CSC.[8,13] Importantly, the circulatory change in MBR correlated with poor visual prognosis and a decrease in the central choroidal thickness with disease regression.[8,14] These observations suggest that choroidal hyperperfusion is involved in the pathogenesis of CSC,[8,13] and MBR is a useful index to evaluate the activity of CSC.

It has been reported that submacular choroid in patients with PPE is

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thick, as it is in CSC[1,2] We recently reported on sequential changes in choroidal thickness in a patient with PPE who developed CSC during follow-up.[5] The submacular choroid was thicker during the alternating onsets of PPE and CSC than those on CSC and PPE regression. These results suggest that choroidal thickening is involved in the pathogenesis of both PPE and CSC.[5] However, the association between choroidal blood flow and the pathogenesis of PPE remains to be fully elucidated. The present study evaluated for the first time, to the best of our knowledge, chronological changes in choroidal circulation hemodynamics using LSFG in two patients with unilateral involvement of PPE and CSC.

2. Findings

2.1. Case 1

A 36-year-old male complained of central visual loss and metamorphopsia in his left eye for 1 week. He had no medical (systemic or ocular), family or psychosocial history, including history of corticosteroid use, episodes of CSC, or smoling habits.

The best-corrected visual acuity (BCVA) was 1.0 OD and 0.8 OS. The Amsler grid test revealed metamorphopsia on the superior side of the center OS. Slit-lamp examination showed no abnormal findings OU. Funduscopy showed normal findings OD and several punctate white subretinal lesions at the center to inferior side of the fovea, but no macular SRD OS (Fig. 1a). Corresponding to the white lesions, hyperfluorescence was observed from the initial phase on fluorescein angiography (FA) and ICGA (Fig. 1b–d). However, late-phase FA revealed no leakage. ICGA showed dilated choroidal veins on the venous phase and CVH at the macula on the middle phase OS (Fig. 1c and d). A vertical image through the fovea on enhanced depth imaging (EDI)-OCT showed discontinuity of the ellipsoid zone (arrowhead), a dome-shaped hyper-reflectivity at the photoreceptor level, and PED above the choroidal pachyvessels, corresponding to the white lesions; however, no macular SRD was detected (Fig. 1e). The central choroidal thickness (CCT) and choroidal thickness (CT) at the lesion site measured 404 and 375 μm, respectively. The patient was diagnosed with PPE OS and was followed-up with no treatment.

Seven months following the initial visit, the patient's BCVA was 1.2 OS with improvement of the metamorphopsia. On EDI-OCT, restoration of the ellipsoid zone was observed, but the appearance of a hyporeflective space between the photoreceptor and the RPE was noted (Fig. 2a). The CCT and CT at the lesion site had decreased to 387 and 359 μm, respectively.

Nineteen months after his initial visit, the patient complained of left central vision loss. Funduscopy showed macular SRD (Fig. 2b), but no leakage was shown on FA. On ICGA, the extent of CVH at the macula had increased further compared with that observed during the initial visit (Fig. 2c). EDI-OCT revealed macular SRD and enlargement of the

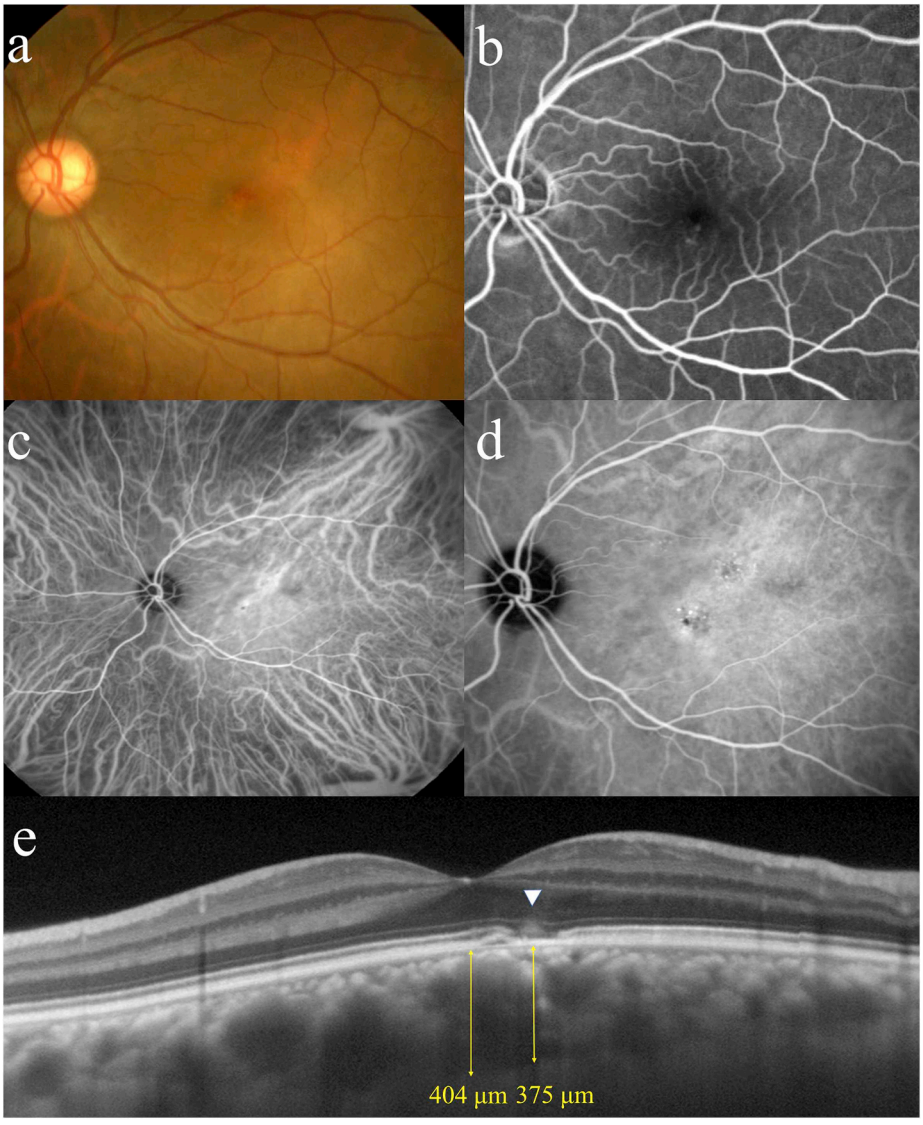

Fig. 1. Photographs of the left eye in a patient with pachychoroid pigment epitheliopathy (PPE) at the initial visit (**a–e**) in Case 1. **a,** Fundus photograph showing several punctate white lesions at the level of the retinal pigment epithelium (RPE) at the fovea, but no serous retinal detachment (SRD). **b–d,** Punctate hyperfluorescence was observed on late-phase fluorescein angiography (FA) (**b**) and on indocyanine green angiography (ICGA) (**c, d**) from the white lesions. However, FA revealed no dye leakage (**b**). ICGA revealed dilated choroidal veins during the venous phase (**c**) and choroidal vascular hyperpermeability of the macula 10 minutes after dye injection (**d**). **e,** Enhanced depth imaging optical coherence tomography (EDI-OCT) image showed a dome-shaped hyper-reflectivity at the photoreceptor level, discontinuity of the ellipsoid zone (arrowhead), and detachment of the RPE corresponding to the white lesions, but no macular SRD was detected. Choroidal pachyvessels were also prominent beneath the macula. Central choroidal thickness (CCT) and choroidal thickness (CT) at the lesion site measured 404 and 375 μm, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

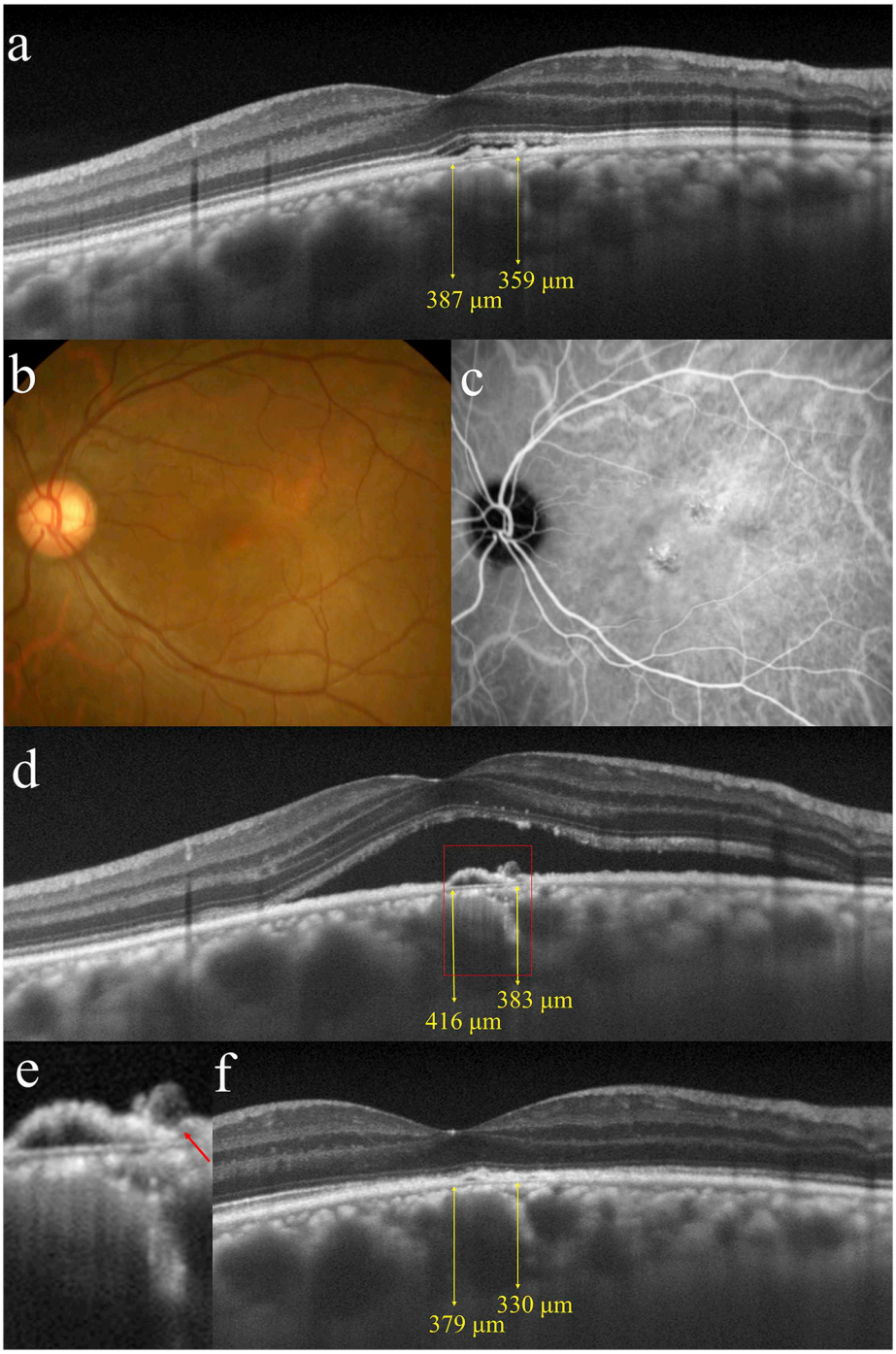

Fig. 2. Photographs of the left eye at improvement of PPE (**a**) and during the onset (**b–e**) and regression (**f**) of central serous chorioretinopathy (CSC) in Case 1. **a,** Seven months later, EDI-OCT showed recovery of the ellipsoid zone corresponding to the lesion. However, dome-shaped hyper-reflectivities of the RPE and a hypo-reflectivity between the interdigitation zone and the RPE appeared. CCT and CT at the lesion site decreased to 387 and 359 μm, respectively. **b-e,** Photographs 19 months after the initial visit. Macular SRD appeared (**b**). On ICGA 10 min post-dye injection, the extent of choroidal vascular hyperpermeability increased compared with that at the initial visit (**c**). EDI-OCT revealed macular SRD with enlargement of RPE detachment. CCT and CT at the lesion site increased to 416 and 383 μm, respectively (**d**). **e,** A magnified view at the fovea of (**d**). An apparent hole of the RPE (arrow) was observed, corresponding to the lesion site of PPE. **f,** Twenty-five months after the initial visit, SRD spontaneously resolved. CCT and CT at the lesion site decreased to 379 and 330 μm, respectively.

PED, with disruption of the RPE corresponding to the site where the PPE lesion was present (Fig. 2d and e). The CCT and CT at the lesion site had increased to 416 and 383 μm, respectively, compared with the values 7 months following the initial visit. The patient was diagnosed with CSC OS. Six months following the onset of CSC, SRD had spontaneously resolved. The CCT and CT at the lesion site had decreased to 379 and 330 μm, respectively (Fig. 2f).

2.2. Case 2

A 43-year-old male PPE patient with no smoking habits developed recurrence of PPE at 25 months and CSC at 35 months in his left eye. The clinical course and changes in CT of this patient have been reported previously.[5]

3. Methods

The present study was approved by the Ethics Committee of Hokkaido University Hospital (#016–0291), Japan. Informed consent was obtained from the patients following explanation of the nature and possible consequences of the study.

3.1. LSFG measurements

LSFG measurements using LSFG-NAVI (Softcare, Fukuoka, Japan) were performed for both eyes three times consecutively between 15-16 o'clock during follow-up in both cases.[12] The mechanism and measurement methods of LSFG have been published previously.[7] On the LSFG color map, circles were set at the fovea to measure the MBR (Figs. 3 and

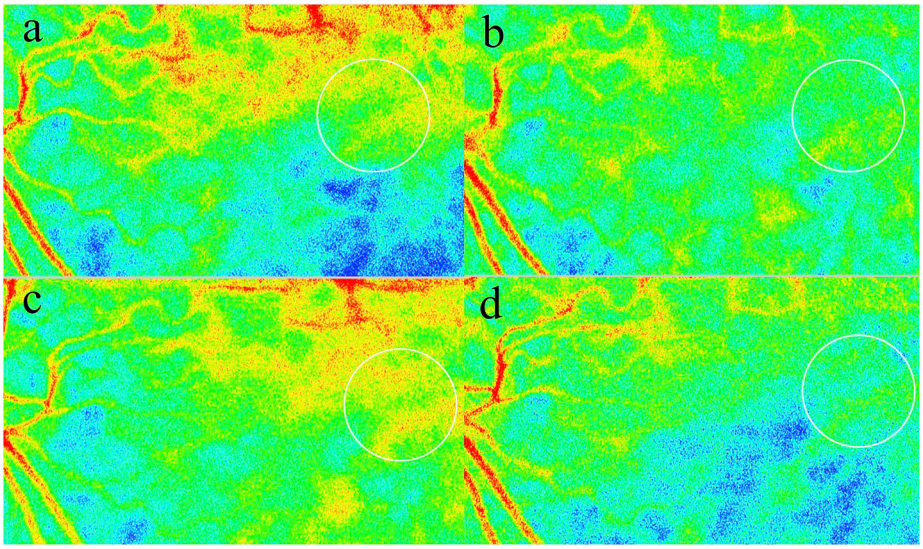

Fig. 3. Color map images of laser speckle flowgraphy in the left eye of Case 1. **a, b,** Images at the initial visit (**a**) and at 7 months (**b**). A circle was set at the fovea to measure the mean blur rate (MBR), a relative index of blood flow velocity. Red indicates a high MBR; blue indicates a low MBR. Macular MBR was 25% higher at the onset of PPE (a) than that on improvement of PPE (b). **c** An image at 19 months. The MBR was 33% higher at the onset of CSC than that on improvement of PPE (b). **e,** An image at 25 months. The MBR was 26% lower on CSC regression than that at the onset of CSC (**d**). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

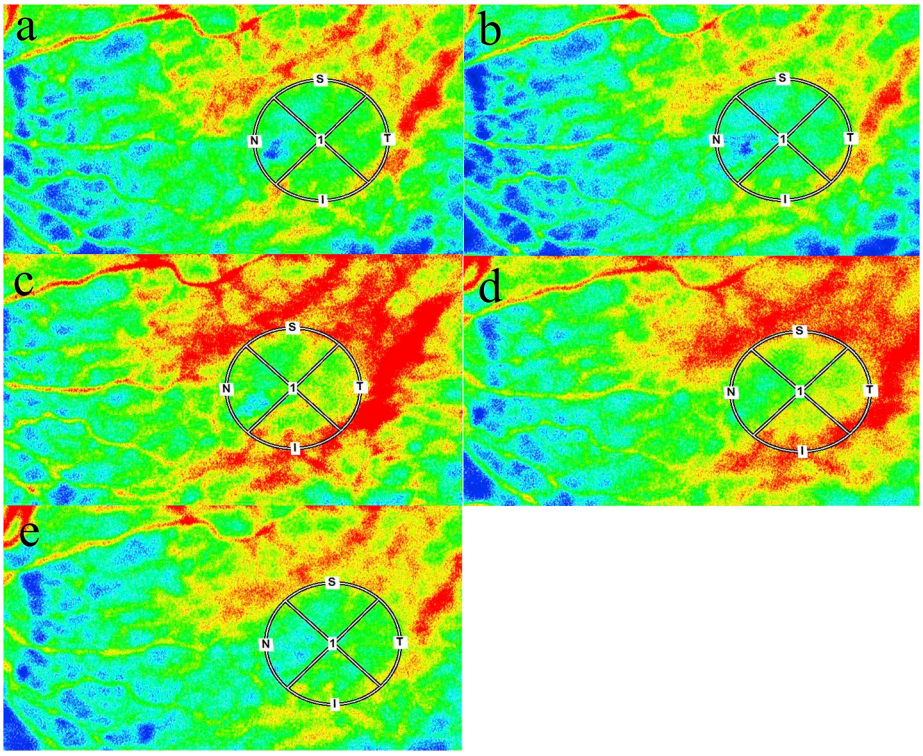

Fig. 4. Color map images of laser speckle flowgraphy in the affected (left) eye of Case 2. **a**, **b,** Images at the initial visit (**a**) and at 19 months (**b**). Macular MBR was 7% lower on the regression of PPE (**b**) than that at the onset of PPE (**a**). **c,** An image at 25 months. The MBR was 21% higher on PPE recurrence than that on PPE regression (**b**). **d,** An image at 35 months. The MBR was 51% higher at the onset of CSC than that on PPE regression (**b**). **e,** An image at 52 months. The MBR was 25% lower on CSC regression than that at the onset of CSC (**d**). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

4) and each MBR within the circles was automatically calculated using LSFG Analyzer software (v 3.0.47; Softcare). The positions of the circles were determined manually by comparing the images of the fundus and the images of the LSFG color map at baseline, and were automatically set at the same site where a circle was set at baseline during the follow-up. Sequential changes in the average MBR were evaluated as the change in the rate of the average MBR against the initial measurement value, as previously described,[8–11] as MBR is a quantitative index of the "relative" blood flow velocity. Two authors (YH, KH), blinded to the patient's clinical information, independently evaluated the LSFG images.

3.2. Hemodynamics

Within a certain range, there is a linear relationship between choroidal blood flow and ocular perfusion pressure (OPP) in healthy subjects.[15] To evaluate the possibility of such physiological responses in the results of the present study, the OPP was calculated from measurements of the patient's blood pressure and intraocular pressure, as described previously.[9]

3.3. EDI-OCT measurement

EDI-OCT measurements (RS-3000 Advance; NIDEK, Gamagori, Japan) were performed for both eyes of Case 1 at the initial visit and 7, 19, and 25 months after the initial visit. Choroidal thickness was determined by manually measuring the distance from the outer border of the hyper-reflective line corresponding to the RPE to the outer border of the choroid (Figs. 1e, 2a, d, f), using a vertical scan through the fovea (scan length, 12.0 mm). Similarly, retinal thickness was measured from the inner limiting membrane to the outer border of the RPE. Thickness

values in the choroid and retina were obtained at the central fovea OU, a PPE lesion site OS, and the same site as the PPE lesion site OD.

4. Results

4.1. LSFG data

In Case 1, the changes in average macular MBR values were as follows: 12.5 ± 0.1, 10.0 ± 0.6, 13.3 ± 1.1, and 9.8 ± 0.3 in the affected eye and 9.1 ± 0.4, 11.3 ± 0.2, 11.1 ± 0.9, and 9.0 ± 0.9 in the fellow eye at the initial visit and at 7, 19, and 25 months after, respectively. Compared with the initial values (100%), the rates of MBR change were 80.0%, 106.4%, and 78.4% at 7, 19, and 25 months after baseline, respectively, in the affected eye (Fig. 3). In the fellow eye, the rates of MBR change were 124.1%, 121.9%, and 98.9% at 7, 19, and 25 months after baseline, respectively. Compared with the macular MBR value on PPE improvement (7 months), the affected eye showed its increases at the onsets of PPE (0 months) and CSC (19 months) by 25% and 33%, respectively, whereas the fellow eye did not have this trend (19% and 2% decreases, respectively).

In Case 2, changes in the average macular MBR values were as follows: 10.5 ± 0.5, 9.8 ± 0.4, 11.9 ± 0.4, 14.8 ± 0.3, and 11.1 ± 0.2 in the affected eye and 15.3 ± 0.9, 12.9 ± 0.7, 14.6 ± 0.7, 14.2 ± 1.1, and 14.3 ± 0.2 in the fellow eye on the initial visit and 19, 25, 35, and 52 months later, respectively. Compared with the initial values (100%), the rates of MBR change were 93.3%, 113.3%, 141.0%, and 105.7% at 19, 25, 35, and 52 months after baseline, respectively, in the affected eye (Figs. 4 and 5). In the fellow eye, the MBR changing rates were 84.3%, 95.4%, 92.8%, and 93.5% at 19, 25, 35, and 52 months after baseline, respectively. Compared with that on PPE regression (19 months), the macular MBR values on PPE recurrence (25 months) and at the onset of CSC (35 months) were increased by 21% and 51%, respectively, in the affected eye and by 13% and 10%, respectively, in the fellow eye (Fig. 5).

4.2. OPP data

In Case 1, the OPP was 18.3, 37.8, 25.8, and 38.1 mmHg on the initial visit and at 7, 19, and 25 months later in the affected eye, respectively. In the fellow eye, the OPP was 18.3, 36.8, 25.8, and 37.1 mmHg on the initial visit and 7, 19, and 25 months later, respectively. In Case 2, the OPP was as follows: 41.0, 41.7, 39.9, and 54.3 mmHg in the affected eye and 41.0, 42.7, 39.4, and 54.9 mmHg in the fellow eye on the initial visit and 19, 25, 35, and 52 months later, respectively. In the affected eyes of both cases, there was no association between the OPP and the changes in MBR.

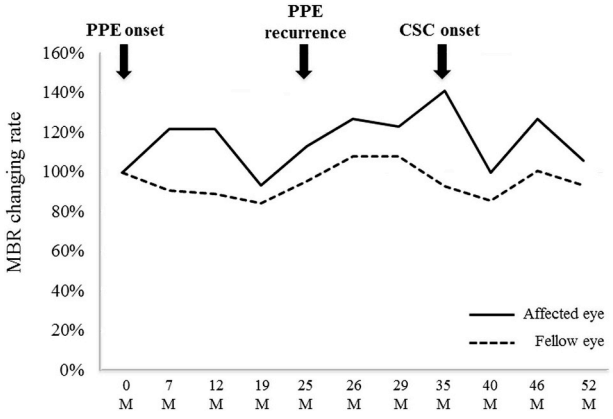

Fig. 5. Graphs of changes in macular MBR in Case 2. When macular MBR values at PPE recurrence (25 months) and the onset of CSC (35 months) were compared with that on PPE regression (19 months), the increased MBR changing rates were higher (21% and 51%, respectively) in the affected eye than those in the unaffected fellow eye (13% and 10%, respectively). The extent of the increased rate of MBR was 2.5 times higher at the onset of CSC than that at the onset of PPE.

4.3. Changes in choroidal thickness

Thickness changes in the choroid and the retina in Case 1 are shown in Table 1. In the affected eye, the choroidal thicknesses at the central fovea and the lesion site were greater than those at the regression of these diseases during the alternate onsets of PPE and CSC (Figs. 1e, 2a, d, f), which was equivalent with the previous data in Case 2.[5] In the unaffected fellow eye, choroidal and retinal thicknesses at both sites were unaltered during the follow-up.

5. Discussion

This study describes two patients with PPE who later developed CSC in the same eyes, revealing the continuity between PPE and CSC as pachychoroid spectrum disorders. We obtained the following results: (1) at the onset of CSC, spots of dye leakage on FA appeared at the same sites as the PPE lesion in both cases; (2) the changing rates of macular MBR at the alternate onsets of PPE and CSC were higher in the affected eye than the values measured on PPE regression or improvement, while these fluctuations were not true with the fellow eye in each case; (3) the observed rates of MBR increase were 1.3–2.5 times higher at the onset of CSC than those at the onset of PPE; (4) the submacular choroid was thicker at the alternate onsets of PPE and CSC and thinner at the regression of these diseases (described previously for Case 2[5]).

In the present cases, the changing rates of macular MBR at the alternate onsets of PPE and CSC were higher in the affected eye than those in the fellow eye. In patients with CSC, an association between increased CT and regions of choroidal hyperpermeability was observed.[16] The average macular choroidal blood flow velocity significantly decreased with regression of CSC and there was a negative correlation between the recovery in BCVA and the reduction of blood flow.[8] These observations suggest the involvement of choroidal hyperperfusion or increased choroidal hydrostatic pressure in the pathogenesis of CSC.[8,16] Therefore, choroidal hyperperfusion is involved in the pathogenesis of both PPE and CSC, and MBR may be useful as a sensitive index for evaluating PPE activity as well as CT. Further investigations with a large number of cases are required to validate our results.

In the two cases described here, the patients developed PPE prior to the onset of CSC. At the onset of CSC, spots of dye leakage on FA were located at the same sites as the PPE lesion in both cases. The observed increases in the rates of MBR were higher at the onset of CSC than those at the onset of PPE, suggesting a potential difference in the severity of choroidal hyperperfusion between CSC and PPE. Therefore, these results indicate that PPE and CSC may occur continuously, and that PPE is a milder subtype of CSC.

Previous studies have revealed that several patterns of disease exist based on different changes in the thickness and blood flow velocity of the choroid during the acute stage of retinochoroidal diseases; an “inflammatory” pattern observed in choroiditis such as Vogt–Koyanagi–Harada disease,[9] acute zonal occult outer retinopathy complex, unilateral acute idiopathic maculopathy, and acute posterior multifocal placoid pigment epitheliopathy[10,11,17–23] (decrease in blood flow and increase in thickness), a “sympathetic” pattern observed in CSC[8,13,14] (increase in both blood flow and thickness), and a “vaso-obstructive” pattern in commotio retinae[24,25] (decrease in both blood flow and thickness). In the present study, the velocity of the macular choroidal blood flow increased in the acute stage of PPE; therefore, the circulatory and morphologic[5] pattern in the choroid was similar to that of CSC. Taken together, our EDI-OCT[5] and LSFG results may validate the hypothesis that PPE and CSC clinically overlap and have a common pathogenic background.[1–3]

Table 1
Choroidal and retinal thicknesses measurements at the macula in a patient with central serous chorioretinopathy associated with pachychoroid pigment epitheliopathy (Case 1).

Measurement site	Choroidal thickness (μm)							
	Right eye (unaffected eye)				Left eye (affected eye)			
	0 M	7 M	19 M	25 M	0 M	7 M	19 M	25 M
Fovea	264	260	251	255	404	387	416	379
PPE lesion site	288	293	280	280	375	359	383	330
	Retinal thickness (μm)							
Fovea	239	239	243	239	214	239	416	173
PPE lesion site	310	317	309	309	305	334	482	222

M, month; PPE, pachychoroid pigment epitheliopathy.

In conclusion, we examined changes in macular choroidal blood flow velocity in patients with PPE who later developed CSC in the same eye. The rates of macular MBR value change in the affected eyes were higher at the alternate onsets of PPE and CSC than the values at PPE regression. In addition, the increased MBR rates observed were 1.3–2.5 times higher at the onset of CSC than those at the onset of PPE. These results support the hypothesis that PPE and CSC clinically overlap and have a common pathogenic background through choroidal hyperperfusion. Therefore, PPE may be a milder subtype of CSC as pachychoroid spectrum disorders.

Patient consent

Informed consent was obtained in writing from the patient for the use of the patient's information for the purpose of this report.

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Authorship

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

Declaration of competing interest

The following authors have no financial disclosures: WS, YH, AK, and SI.

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