



Pigment Epithelial Detachment and Leak Point Locations in Central Serous Chorioretinopathy

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• **PURPOSE:** To examine the associations between the vortex vein characteristics and locations of the pigment epithelial detachment (PED) and leak point in patients with central serous chorioretinopathy (CSC).

• **DESIGN:** Observational case series.

• **METHODS:** We evaluated 116 eyes of 104 patients with CSC. The PED and leak point locations were superimposed over the choroidal *en face* images using widefield swept-source optical coherence tomography and fluorescein angiography. We defined the draining areas of the superior and inferior vortex veins and analyzed their associations with the PED and leak point locations.

• **RESULTS:** One of the 116 eyes with a unique irrigation pattern dominated by the nasal vortex vein was excluded from the analysis. Sixty-nine (60%) of the remaining 115 eyes exhibited asymmetry between the superior and inferior vortex veins. PEDs and leak points were in the vortex vein draining area with greater dilation in 66 (96%) of 69 eyes with asymmetry, and none (0%) were in the opposite areas. Both the PEDs and leak points showed significant differences in their distributions ($P < .001$, respectively). Additionally, 74% of PEDs and 84% of leak points were located upstream of the vortex vein draining areas, whose frequency was significantly higher compared to other areas ($P < .001$, respectively).

• **CONCLUSION:** PED and leak point spatial distributions corresponded with the most terminal part of the dilated vortex veins, suggesting that blood flow disturbances, such as stasis within the affected vortex veins, may be essential in the pathogenesis of CSC. (Am J Ophthalmol 2024;261: 19–27. © 2024 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>))

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INTRODUCTION

CENTRAL SEROUS CHORIORETINOPATHY (CSC), which is a leading cause of visual impairment in young to middle-aged individuals,¹⁻³ is characterized by the accumulation of subretinal fluid (SRF) at the posterior pole of the eye.¹⁻⁵ The origin of this SRF can be traced to leak points in the retinal pigment epithelium (RPE) layer.^{2,6,7} Pigment epithelial detachment (PED), often observed within or adjacent to the SRF area, is thought to represent an intermediate stage during which SRF leaks from the choriocapillaris into the subretinal space.^{8,9} Although some studies suggest an association between the fovea and the locations of the PED and leak point,^{2,10-12} others indicate that these leak points could often be located considerably far from the fovea.^{7,12,13} The reason for this distribution pattern remains elusive.

Numerous studies have revealed the substantial contribution of choroidal vascular abnormalities to the pathogenesis of CSC.^{5,14-19} Previous studies have stated that the location of the PEDs often aligns with the leak point as identified on fluorescein angiography (FA) and with choroidal hyperfluorescent regions on indocyanine green angiography (ICGA).^{8,20-22} Technological strides in optical coherence tomography (OCT), especially enhanced depth imaging (EDI), *en face* imaging, and the inception of swept-source (SS) OCT, have enhanced our ability to scrutinize the choroidal vasculature, unveiling critical pathologies affiliated with CSC.^{5,16,17,23-26} A study employing widefield OCT data posited that PEDs did not necessarily occur at the point of greatest choroidal thickening.²⁷ Although assessing choroidal thickness, which comprises vascular as well as stromal components provides valuable insights,^{28,29} sole reliance on this metric may not offer a comprehensive view of the vascular features. On the contrary, choroidal *en face* imaging presents the vortex vein characteristics in richer detail.^{5,13,25,30-33}

In this study, we meticulously analyzed widefield SS-OCT chorioretinal data of eyes with CSC, endeavoring to decipher the association between the vortex vein features on choroidal *en face* imaging and the locations of the PED and leak point.

PATIENTS AND METHODS

- **PATIENTS:** This observational study was approved by the Institutional Review Board of Kyoto University Graduate School of Medicine and conformed with the tenets of the Declaration of Helsinki. Written informed consent was secured from each participant prior to any study-related procedures or examinations.

This study enrolled consecutive patients with treatment-naïve CSC and SRF at the macula who visited the Department of Ophthalmology of Kyoto University Hospital between October 2021 and March 2023. The diagnosis of CSC was based on the presence of SRF at the posterior pole, which was further verified by dye leakage from the RPE during FA and visualization of focal choroidal vascular hyperpermeability during late-phase ICGA.

Patients were excluded if they had other chorioretinal diseases accompanied by SRF, eyes with conditions such as macular neovascularization, drusenoid PED, hemorrhagic PED, pit-macular syndrome, uveitis, scleritis, and ocular hypertension (> 21 mmHg) or hypotension (< 5 mmHg). Additionally, patients with a history of anti-vascular endothelial growth factor therapy, surgery (except cataract surgery), photodynamic therapy, direct photocoagulation, or corticosteroid administration were not included. The other exclusion criteria were keratoconus, high myopia with a spherical equivalent < -6 D, hyperopia $> +4$ D, astigmatism $> \pm 3$ D, pregnancy, and low-quality OCT images (signal strength index < 5) due to eye movement or media opacities.

During the initial consultation, each patient underwent a thorough ophthalmic evaluation, including refraction, decimal best-corrected visual acuity (BCVA) testing using the 5-m Landolt chart, intraocular pressure, and axial length measurements. We also conducted slit-lamp biomicroscopy, color fundus photography, FA, ICGA, fundus autofluorescence photography, and SS-OCT. Refraction was gauged objectively using an autorefractor (ARK-530A, NIDEK, Gamagori, Japan). The spherical equivalent was computed as the sum of the spherical power and half of the cylindrical power. Axial length measurements were conducted using an interferometer (IOL Master 700; Carl Zeiss Meditec, Dublin, CA, USA). Meanwhile, color fundus photographs were captured using a dedicated fundus camera system (TRC50LX, Topcon Corp., Tokyo, Japan). Both FA and ICGA were performed using a 55°-span confocal-scanning laser ophthalmoscope (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany).

- **EVALUATION OF PED USING CHOROIDAL EN FACE IMAGES BY EDI OF WIDEFIELD SS-OCT:** Chorioretinal structures were evaluated using SS-OCT (Xephilio OCT-S1, Canon Inc., Otawara, Japan), which boasted an illumination range of 1010 to 1110 nm and a scanning speed reach-

ing 100,000 A-scans per second. We set the OCT focusing spot at 30 mm, ensuring an expansive scan area without the need for supplementary lenses or alterations to the device.

We acquired 3-dimensional volume data of 20 mm (vertical, 128 B-scans) $\times$ 23 mm (horizontal, 1024 pixels) $\times$ 5.3 mm (scan depth, 1396 pixels) using the EDI mode of SS-OCT to create PED maps and choroidal *en face* images within the posterior pole. The space nestled between the outer surface of the RPE and Bruch's membrane was denoted as the PED layer. Conversely, the choroid was identified as the layer sandwiched between Bruch's membrane and the chorioscleral boundary. Our analysis only encompassed PEDs that manifested on a minimum of 2 OCT B-scan images. Additionally, PEDs that were separated by less than 2 OCT B-scan images were deemed a single unit. We excluded lesions that resembled drusen in color fundus photography. While the segmentation process relied heavily on automation via artificial intelligence-backed software, we resorted to manual adjustments when deemed imperative.

- **LOCATION OF THE PEDS AND LEAK POINTS:** To accurately determine the locations of the leak points, we identified a pinpoint RPE defect on FA, characterized by an increasing area of hyperfluorescence over time, which is a classical feature of acute CSC,⁷ for use as the reference leak point in this study.

To precisely map the locations of the PED and leak point, the PEDs delineated by SS-OCT and leak points captured on FA were superimposed over the choroidal *en face* images (Figure 1) using the ImageJ software ver. 1.51 (Wayne Rasband, National Institutes of Health, Bethesda, MD, USA; <http://rsb.info.nih.gov/ij/index.html>).

Based on previous studies,^{10,12} we assessed the distance and relative positional relationships of the PED and leak point with respect to the fovea.

Following this evaluation, we evaluated the locations of the PED and leak point to determine whether they were located within the draining area of either the superior or inferior vortex vein. During this assessment, areas that were not distinctly localized to either the superior or inferior draining areas were designated as the borderline zone. All areas, excluding the borderline zone, were classified into their respective vortex vein-draining areas. Additionally, based on the methodology of previous studies,^{14,23} the symmetry between the superior and inferior vortex veins was evaluated using *en face* OCT. In cases of asymmetry, we identified the dominant and non-dominant sides based on the method of the previous report.²³ Subsequently, we assessed the presence of the PED or leak point in either the upstream or mid/downstream draining area of the vortex veins for each eye. To ensure objectivity and minimize potential biases, these evaluations were conducted independently by 2 retinal specialists (TK and NN). Any discrepancies between their assessments were resolved via discussion or, if needed, consultation with a third specialist (YM).

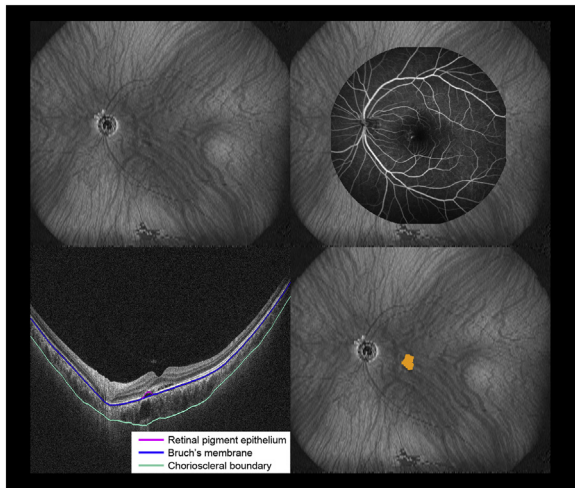


FIGURE 1. Identification of the location of the leak points and pigment epithelial detachments (PEDs) using widefield swept-source optical coherence tomography in patients with central serous chorioretinopathy. (Top Left) *En face* image of the choroid with a scanning area of 20 mm vertically $\times$ 23 mm horizontally. (Top right) The locations of the leak points were projected onto the corresponding *en face* image using 55° fluorescein angiography images. (Bottom left) The PED layer was defined as the space enclosed between the outer surface of the RPE and Bruch's membrane. (Bottom right) The map of the PED layer (orange) was projected over the corresponding *en face* image. RPE: retinal pigment epithelium.

Cases where the pathological feature of interest was in the inferior vortex vein draining area were inverted to acquire an in-depth understanding of the PED and leak point relative to the vortex vein draining areas. This permitted an accurate assessment of their relative position with respect to the macula and optic disk in the draining area.

Additionally, we adopted the segmentation approach used by previous studies^{24,34} to comprehensively and objectively evaluate the location of the PEDs and leak points. We partitioned the area into 4 distinct sections using the optic disk-fovea line and a vertical line through the optic disk, which served as the boundary lines for the vortex veins.^{24,34} We classified the PEDs and leak points as located in the borderline zone as the “B-zone group,” those located in the vortex vein draining area upstream segment of the vortex veins beyond the boundary lines as the “D-up group,” and those in the vortex vein draining area downstream segment relative to the boundary lines as the “D-down group.” In the D-down group, distances from each quadrant boundary line were recorded. To determine the distances from both the fovea and these boundary lines, we employed the Bennett procedure, a modified version of the Littmann formula, ensuring adjustment for magnification related to the axial length.^{35,36}

• **STATISTICAL ANALYSIS:** All data were analyzed using JMP Statistics version 16.0 Pro. Values were presented as

the mean $\pm$ standard deviation. BCVA values derived from the Landolt chart were converted to the logarithm of the minimum angle of resolution units. The chi-squared test was utilized to determine the vortex vein draining area with the highest frequency of PEDs and leak points. *P*-values $< .05$ indicated statistical significance.

RESULTS

• **PATIENT DEMOGRAPHICS AND GENERAL FINDINGS:** We analyzed 116 eyes of 104 patients diagnosed with CSC, of whom 73 were men and 31 were women (Table 1). Among them, 40 eyes presented with visual symptoms within 6 months. Each eye exhibited PEDs, leak points, or both. We identified 77 leak points in 61 eyes and 314 PEDs in 114 eyes. One eye presented with a rare dominance of the nasal vortex vein in the macular region, leading to PED formation (Supplementary Figure 1). Given that this pattern was seldom observed in the current and previous studies,^{24,31,34,37} our analysis focused primarily on the remaining 115 eyes.

• **LOCATION OF THE PEDS AND LEAK POINTS RELATIVE TO THE FOVEA:** Figure 2 depicts the spatial distributions of the PED and leak point with respect to eye laterality and their proximity to the fovea and optic disk. The prevalence of PEDs diminished as the distance from the fovea increased. However, the majority of leak points were located within 1 to 2 mm from the fovea, followed closely by those within 0 to 1 mm. Specifically, 33% of PEDs and 32% of leak points were identified within the immediate 1 mm radius of the fovea. We observed an elongated broad distribution, extending to or beyond the fovea; 61% of the PEDs and 72% of the leak points within this 1 mm radius were located on the nasal side.

• **ASSOCIATION BETWEEN THE DRAINING VORTEX VEINS AND LOCATIONS OF THE PEDS AND LEAK POINTS:** A significant number of eyes displayed PEDs in the upstream segment of the vortex veins (Figure 3). Ninety-three (81%) of the 115 eyes manifested PEDs in the draining areas of either the superior or inferior vortex veins. The leak points corresponded with most PED locations. In contrast, 18 eyes (16%) exclusively exhibited leak points in the borderline zone. Four eyes (3%) demonstrated PEDs and leak points in both draining areas, with both superior and inferior dilated vortex veins (Supplementary Figure 2). The PEDs were situated in the superior vortex vein draining area in a significantly higher number of eyes compared to the inferior one ($P = .016$; Table 2). Among the cases with vortex vein asymmetry (69 eyes), the PEDs and leak points were located in the vortex vein draining area with greater dilation in 66 eyes (96%), and none (0%) in the opposite areas. The remaining 3 eyes (4%) displayed PEDs and leak points

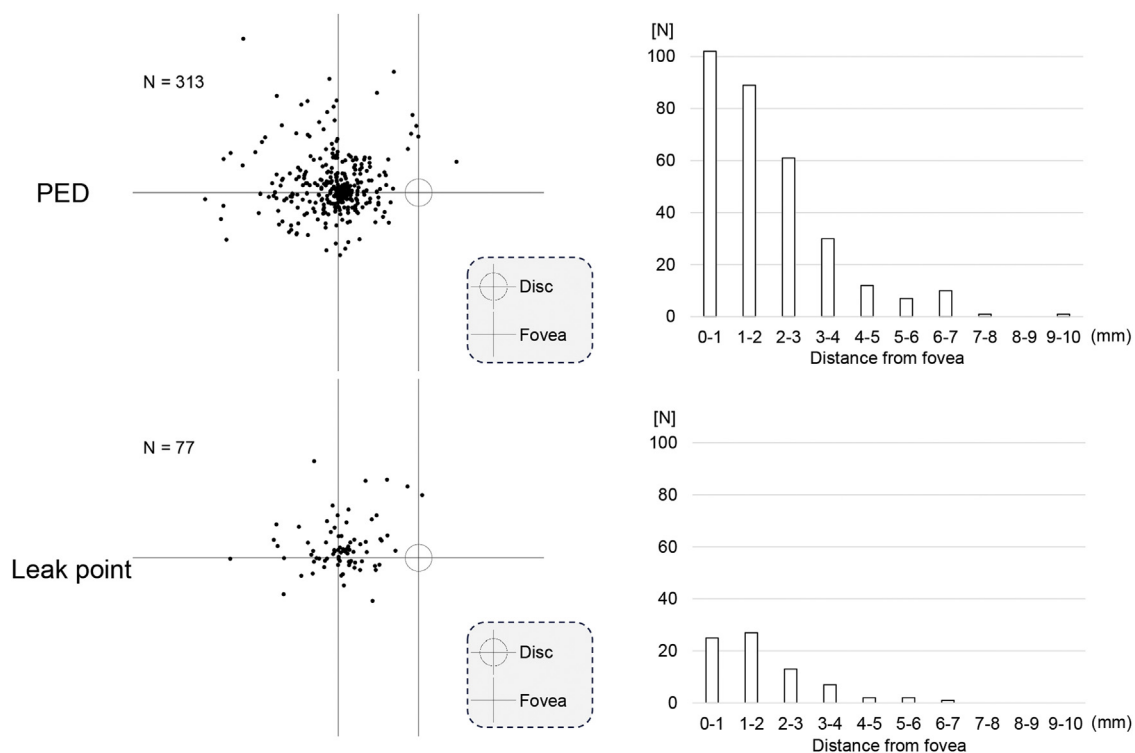


FIGURE 2. Relative locations of the pigment epithelial detachment (PED) and leak point to the fovea. (Left) Relative locations of the PEDs and leak points to the fovea and optic disk. (Right) Distribution of the distances between the fovea and the locations of PEDs and leak points: PED distribution decreases as the distance from the fovea increases, while the leak point distribution peaks at 1 to 2 mm, closely followed by the 0 to 1 mm range. Only 33% of PEDs and 32% of leak points are found within the first 1 mm from the fovea. Notably, 61% of PEDs and 72% of leak points within this range are nasally localized.

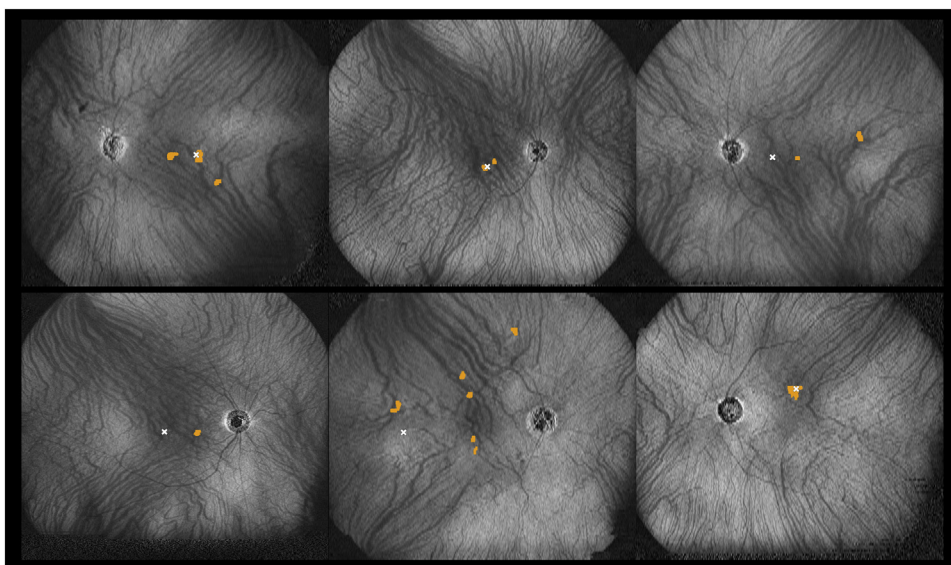


FIGURE 3. Representative cases with pigment epithelial detachments (PEDs) and leak points. In most cases, PEDs (orange) and leak points (white crosses) were found in the area upstream of the superior or inferior vortex veins. In cases with vertical asymmetry of the vortex veins, PEDs and leak points have a tendency to occur in the dominant vortex vein draining area.

TABLE 1. Characteristics of Patients With Central Serous Chorioretinopathy

Number of patients (men/women)	104 (73/31)
Number of eyes (men/women)	116 (85/31)
Mean age, years (range, years)	58.1 ± 13.0 (24-85)
Axial length, mm (range, mm)	23.8 ± 0.8 (21.6-25.5)
Best-corrected visual acuity in logMAR (Snellen equivalent)	0.03 ± 0.21 (20/100-20/13)
Duration of the symptom, months (range, months)	38.7 ± 54.4 (0.1-280)
Number of leak points per eye	0.7 ± 0.7 (0-2)
Number of pigment epithelial detachments per eye	2.7 ± 2.0 (0-11)

Data are presented as the mean ± standard deviation, unless otherwise indicated.
LogMAR = logarithm of minimum angle of resolution.

TABLE 2. Pigment Epithelial Detachment and Leak Point Locations With Respect to Vortex Vein Characteristics

<i>N</i> = 115 Eyes	Superior Vortex Vein Draining Area	Inferior Vortex Vein Draining Area	<i>P</i> Value
Eyes with PED, <i>n</i>	57	39	.016
Eyes with leak point, <i>n</i>	32	20	.058
Eyes with asymmetry, <i>n</i> = 69	Dominant side	Nondominant side	<i>P</i> value
Eyes with PED, <i>n</i>	66	0	<0.001
Eyes with leak point, <i>n</i>	37	0	<0.001
<i>N</i> = 115 eyes	Upstream	Mid- or downstream	<i>P</i> value
Eyes with PED, <i>n</i>	85	26	<0.001
Eyes with leak point, <i>n</i>	49	5	<0.001

PED = pigment epithelial detachment.

Comparisons between each domain were performed using the chi-squared test for the presence or absence of PEDs and leak points.

within the borderline zone. The distributions of the PEDs and leak points exhibited significant differences ($P < .001$, respectively; Table 2). Additionally, there was a significant tendency for PEDs and leak points to be situated upstream of the vortex vein draining areas ($P < .001$, respectively; Table 2).

• **OBJECTIVE ASSESSMENT OF PED AND LEAK POINT LOCATIONS:** Figure 4 illustrates the PEDs and leak points with respect to vortex vein drainage. Both PEDs and leak points exhibited an elongated band-like distribution pattern.

Seventy-four percent of the PEDs were predominantly situated near (within 0-1 mm) or in the upstream segment beyond the quadrant boundary lines. Similarly, 84% of leak points were situated near or in the upstream segment beyond these boundary lines (Figure 4).

Figure 5 depicts the differences in the results based on the symmetry or asymmetry of the superior and inferior vortex veins. Among the PEDs in draining areas with asymmetrical vortex veins, 42% were situated in the upstream segment beyond the quadrant boundary lines (D-up group), while 30% were situated near these boundary lines. Conversely, 42% of PEDs in draining areas with symmetrical

vortex veins were situated in the borderline zone (B-zone group), and 25% were situated near the boundary lines.

Similarly, 77% of leak points in draining areas with asymmetrical vortex veins were situated near or in the upstream segment beyond the quadrant boundary lines. In areas with symmetrical vortex veins, 72% of leak points were situated in the borderline zone or near the boundary lines.

DISCUSSION

Our research highlighted the association between the PED and leak point spatial distributions in CSC and the characteristics of vortex vein traits using widefield SS-OCT. Specifically, we observed a tendency for PEDs and leak points to be located in the upstream segment of the dominant vortex veins.

Central serous chorioretinopathy has been acknowledged since its initial identification in von Graefe's 1866 study.³⁸ Traditionally, CSC was perceived as a macular disease.^{7,10} However, the evolution of imaging technologies, notably the introduction of EDI and widefield SS-

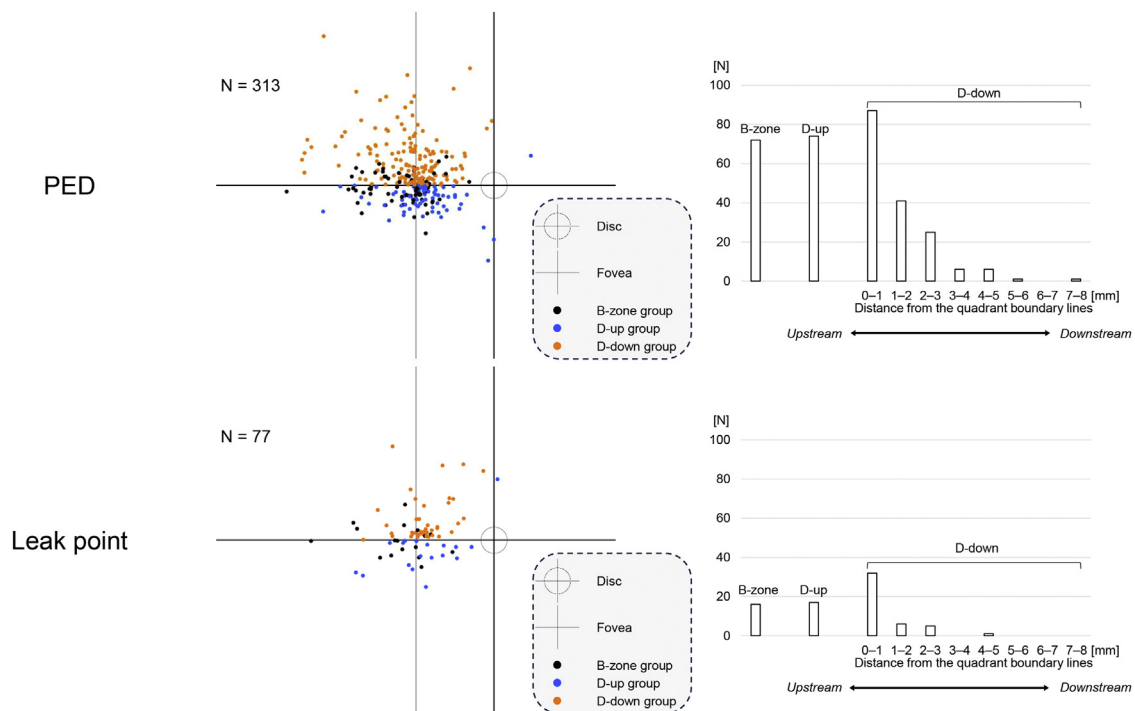


FIGURE 4. Locations of the pigment epithelial detachment (PED) and leak points relative to the vortex vein draining area. (Left) PED and leak point locations with respect to the vortex vein drainage, after adjusting the data by converting the positions of the inferior vortex vein to correspond with those of the superior vortex vein. We classified PEDs and leak points located in the borderline zone as the “B-zone group,” those in the draining area upstream of the vortex veins beyond the boundary lines as the “D-up group,” and those in the vortex vein draining area downstream segment relative to the boundary lines as the “D-down group.” Both PEDs and leak points exhibited a band-like pattern along the optic disk-fovea line. (Right) The distribution of the distances between the boundary lines (the optic disk-fovea line and a vertical line through the optic disk) and the locations of PEDs and leak points. A no Table 74% of PEDs and 84% of leak points are concentrated near (within 0-1 mm) or in the upstream segment beyond the boundary lines.

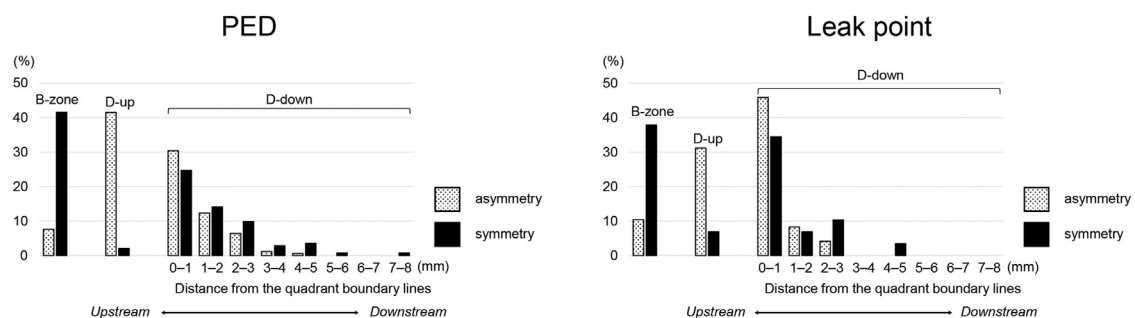


FIGURE 5. Distribution of PEDs and leak points with respect to vortex vein symmetry. In cases with asymmetry, PEDs were most frequently situated in the upstream segment beyond the quadrant boundary lines, which were categorized as the d-up group (42%), followed by those within 0 to 1 mm from these boundary lines, which were categorized as the d-down group (30%). In cases with symmetry, PEDs were found most frequently in the borderline zone, which were categorized as the B-zone group (42%), followed by those within 0 to 1 mm from the boundary lines, which were categorized as the d-down group (25%). In both scenarios, the upstream groups accounted for the majority of PEDs. Leak points in cases with asymmetry were predominantly situated near (within 0-1 mm from) or in the upstream segment beyond the quadrant boundary lines, categorized as the d-down or d-up group, respectively, accounting for 77% of them. In cases with symmetry, the majority of leak points were situated in the borderline zone or near (within 0-1 mm from) the boundary lines, categorized as the B-zone or d-down group, respectively, accounting for 72% of them. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

OCT, has underscored the pivotal role of vortex vein characteristics in understanding the pathophysiology of CSC.^{5,16,17,23-26}

Central to understanding CSC is the fact that the SRF originates from leak points in the RPE layer.^{1,7,9} The prevalent belief is that these leak points often coincide with or are in close proximity to the site of PED.⁸ Data acquired from FA have elucidated that leak points in CSC predominantly appear near the fovea, especially nasally.¹² This pattern is mirrored in PEDs.¹⁰ Additionally, studies have noted that not all leak points are concentrated within 0.5 mm from the fovea.^{12,13} The reason behind this distribution pattern was uncertain. In this study, most PEDs and leak points were concentrated around the fovea, particularly on the nasal side. These findings closely align with the results of previous studies that utilized FA.

The choroidal vasculature, especially vortex veins, has been a focal point in attempts to understand the pathophysiology of CSC. Prior studies have reported choroidal vessel dilation at macular leak points on OCT B-scan images.⁶ In contrast, Kim and associates, using widefield SS-OCT, revealed that PEDs typically appeared closer to the fovea than to the area of maximal choroidal thickness.²⁷ This might indicate that PEDs observed in CSC might not be directly attributable to choroidal thickening alone. In light of this hypothesis, our study employed widefield choroidal *en face* images to further investigate the pathogenesis of CSC, with particular attention to the vortex vein characteristics.

The course of the vortex vein shows significant variability among individuals. It is widely understood that the macula typically falls within the area of drainage served by the temporal vortex veins.^{24,31,34,37} These veins extend from the periphery to the line between the optic disk and the macula, located nasally to the fovea.^{34,37} We considered that the topography, where the area nasal to the fovea is upstream of the temporal vortex veins, could account for both our findings and historical observations of PEDs and leak points located primarily near the macula, especially on the nasal side.

In the majority of the eyes examined, PEDs and leak points were situated within the draining areas of either the superior or inferior vortex veins. Notably, PEDs and leak points were infrequently observed in the borderline zone between the draining areas of the superior or inferior vortex veins. Furthermore, in cases that exhibited vortex vein asymmetry, PEDs and leak points were located in the vortex vein draining area with greater dilation in the vast majority of eyes, with none observed in the opposite areas. This observation strongly underscores the significance of the relationship between vortex vein traits and the location of PEDs and leak points.

Close observation of cases with vortex vein asymmetry revealed that most PEDs and leak points were located near the optic disk-macula line or in a more upstream segment

of the vortex veins beyond this line. In cases with symmetry, most of the PED and leak points were located near the upstream end of the vortex veins, corresponding to the area around the borderline zone. Thus, irrespective of the vortex vein patterns, PED and leak points frequently appeared upstream of the affected vortex veins. These findings suggest that the development of SRF in CSC is influenced not just by the morphological characteristics of the vortex veins, such as dilation and asymmetry, but also by impaired blood flow within these altered veins. We speculate that such disturbances in venous flow, potentially manifesting as stasis or overload, may underlie the emergence of both SRF and PED in CSC within the affected vortex veins. This viewpoint aligns well with recent theories¹⁴⁻¹⁸ on the pathogenesis of CSC.

Systemic factors, including stress,³⁹ type A behavior,⁴⁰ being male,³ pregnancy,⁴¹ corticosteroid use,⁴² have long been implicated in the development of CSC. Corticosteroids are known to suppress cell adhesion molecule expression.⁴³ Corticosteroids and susceptibility genes such as TNFRSF10A and GATA5 may be related to RPE dysfunction and choroidal vascular involvement.⁴⁴ Although their precise role remains uncertain, our study underscored the significant association of morphological and functional (blood flow) changes in the vortex veins with the pathophysiology of CSC. Structural abnormalities, such as pachychoroid, may enhance choroid and RPE junction vulnerability to leakage. It is unclear if systemic factors directly influence these local changes or act independently. However, disturbances in vortex vein blood flow seem pivotal in the onset of CSC.

This research was beset by some limitations. Variation in postonset periods, potential compromise in OCT image detail due to the widefield view, potential oversight of the finer extent of the vortex veins, and the limited scope of cases with SRF detected in the fovea are challenges that warrant acknowledgment. Our evaluation focused solely on leakage arising from pinpoint RPE defects, and other patterns of RPE leakage, such as diffuse leakage, were not assessed in this study. The cross-sectional nature of our approach could not account for the temporal progression of PEDs and leak points. However, our observations indicate a clear link between the characteristics of vortex veins and the emergence of PEDs and leak points.

In conclusion, our study provides compelling evidence that key pathologies such as leak points and PEDs are predominantly found in the most upstream regions of the dilated vortex veins in CSC. These findings are consistent with recent hypotheses emphasizing the role of blood flow disturbances such as stasis or overload within these affected vortex veins in the development of CSC. The use of widefield imaging in our research not only deepens our understanding of the relationship between choroidal circulation and CSC pathology but also paves the way for further studies into other pachychoroid spectrum disorders.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

TAKAHIRO KOGO: Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **YUKI MURAOKA:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **MASAHARU ISHIKURA:** Writing – review & editing, Resources, Investigation. **NAOMI**

NISHIGORI: Writing – review & editing, Resources, Investigation. **YUKI AKIYAMA:** Writing – review & editing, Resources, Investigation. **NAOKO UEDA-ARAKAWA:** Writing – review & editing, Resources, Investigation. **MANABU MIYATA:** Writing – review & editing, Resources, Investigation. **SOTARO OOTO:** Writing – review & editing, Resources, Investigation. **MASAYUKI HATA:** Writing – review & editing, Resources, Investigation. **AYAKO TAKAHASHI:** Writing – review & editing, Resources, Investigation. **MASAHIRO MIYAKE:** Writing – review & editing, Resources, Investigation. **AKITAKA TSUJIKAWA:** Writing – review & editing, Resources, Investigation, Funding acquisition.

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