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Clinical characteristics of peripheral exudative hemorrhagic chorioretinopathy easily misdiagnosed at initial presentation in Korean patients

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Few studies have comprehensively examined the clinical features of peripheral exudative hemorrhagic chorioretinopathy (PEHCR) due to its low prevalence. This study analyzed the clinical characteristics of patients diagnosed with PEHCR at a single center in Korea. We conducted a retrospective review of patient records from November 2005 to December 2020. The cohort included 36 patients (43 eyes), with a mean age of 70 years, and 67% were female. The mean initial best-corrected visual acuity was 0.95 logMAR (Snellen equivalent, 0.11). The most common initial symptom was decreased visual acuity, followed by floaters and visual field defects, while 26% of patients reported no ocular symptoms. Lesions were predominantly located in the inferotemporal (58%) and superotemporal quadrants (51%), with exudations being the most prevalent finding (65%). More than half of the patients (56%) were initially misdiagnosed with choroidal melanoma, while only 8% received the correct diagnosis of PEHCR. Of the 37 eyes (86%) that received treatment, 57% received anti-vascular endothelial growth factor injections, and 19% underwent vitrectomy. PEHCR is a rare degenerative condition with varied presentations in the peripheral retina, often leading to misdiagnosis and delayed treatment. Thus, careful monitoring and appropriate management are essential to minimize the risk of vision-threatening complications.

Keywords Peripheral exudative hemorrhagic chorioretinopathy, Clinical characteristics, Asian population, Observational study

Peripheral exudative hemorrhagic chorioretinopathy (PEHCR) is a rare clinical entity characterized by hemorrhage and exudates in the peripheral retina[1]. It was first described by Reese and Jones in 1962 as hemorrhagic choroidal lesions similar to those seen in age-related macular degeneration located in the peripheral retina[2]. Subsequent studies have reported that PEHCR mainly affected older Caucasian women, with bilateral involvement in approximately 30% of patients[3,4]. Lesions were located mainly in the inferotemporal quadrant, with a mean basal dimension of 10.1 mm[4]. Its major known risk factors include age and hypertension, with most frequent disease presentation at 77–83 years of age and a reported incidence of hypertension of 51–55% among these patients[4,5].

Because the clinical features of PEHCR are similar to those of other retinal disorders, such as uveal melanoma or other choroidal tumors, it might be difficult to differentiate it from these diseases[6,7]. However, as the prognosis and management of PEHCR markedly differ from those of choroidal tumors, timely and accurate identification of PEHCR is crucial[5,8]. The vast majority of PEHCR lesions stabilize or regress spontaneously; therefore, regular observation is recommended in asymptomatic patients[4]. In the event of visual impairment accompanied by subfoveal extension of subretinal fluid or vitreous hemorrhage, anti-vascular endothelial growth factor (VEGF) injection or vitrectomy may be considered as treatment options[8].

PEHCR is extremely rare among people of Asian descent. In a study by Shields et al., only two Asian patients among 146 patients had PEHCR[4], which supported the findings of Annesley, who reported that PEHCR mainly occurred in Caucasians based on a study involving 1 African-American and 26 Caucasian patients[3]. Owing to its

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low prevalence, the current knowledge on the clinical features of PEHCR in Asian patients is scarce and based primarily on published case reports.

Therefore, the main objective of this study was to report the clinical characteristics of PEHCR through analysis of all patients diagnosed with this condition over a 15-year period at a tertiary referral center in Korea.

Methods

This study was approved by the Institutional Review Board of our institution (Yonsei University Gangnam Severance Hospital Institutional Review Board; approval No. 3-2023-0176), and it complied with the principles of the Declaration of Helsinki. Owing to its retrospective nature, informed consent was waived by Yonsei University Gangnam Severance Hospital Institutional Review Board.

We retrospectively reviewed anonymized medical records of patients diagnosed with PEHCR between November 1, 2005, and December 31, 2020, at our institution in Korea. The inclusion criterion was the establishment of a PEHCR diagnosis by a senior retina specialist. The exclusion criteria included coexistence of other retinal diseases not related to PEHCR, a follow-up period of less than 1 year, and insufficient clinical history.

The collected data included patient demographics, medical history, initial diagnosis, ocular symptoms and findings, and treatment. All patients underwent thorough ophthalmological evaluation, including slit lamp examination, fundus examination, optical coherence tomography (OCT), fluorescein angiography (FA), and indocyanine green angiography (ICGA).

Best-corrected visual acuity (BCVA) was reported in Snellen notations and converted to logarithm of the minimum angle of resolution (logMAR) units for statistical analysis. To analyze the distribution of BCVA changes, patients were categorized into three groups according to the BCVA at the initial visit, as follows: ≤0.30 logMAR, between 0.30 and 1 logMAR, and >1 logMAR. BCVA levels of counting fingers, hand motion, light perception, and no light perception were converted to 2.3, 2.6, 2.9, and 3.2 logMAR, respectively. Data were presented as mean ± standard deviation and were analyzed using the Wilcoxon test. P-values < 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics ver. 21.0 (IBM Corp., Armonk, NY, U.S.A.).

Results

A total of 36 patients (43 eyes) were included in this study. Patients' baseline characteristics are summarized in Table 1. Their overall mean age was 70 (range, 18–87) years, and the majority of patients were women (67%). Bilateral involvement was reported in only seven (19%) patients. The mean follow-up duration was 2.9 ± 3.0 years, and the mean duration from the first hospital visit to disease diagnosis was 4.0 ± 8.1 months. The most frequent comorbidities were hypertension ($n = 24$, 67%), followed by diabetes ($n = 9$, 25%) and systemic malignancy ($n = 8$, 22%). Decreased BCVA was the most prevalent initial symptom (42%), followed by floaters (16%) and visual field defects (9%), while 26% of patients had no ocular symptoms at the first visit. The mean BCVA at the initial visit was 0.95 logMAR (Snellen equivalent, 0.11), with values of ≤0.30 logMAR in 18 eyes (42%), between 0.30 and 1 logMAR in 10 eyes (23%), and >1 logMAR in 15 eyes (35%).

On fundus examination (Table 2), most lesions were located in the inferotemporal ($n = 25$, 58%) and superotemporal ($n = 22$, 51%) quadrants. The most common findings in the peripheral retina were exudations (observed in 65% of cases), followed by subretinal and subretinal pigment epithelium (sub-RPE) hemorrhage and vitreous hemorrhage in 54% and 42% of cases, respectively (Fig. 1a). The macular OCT, FA, and ICGA findings are described in Table 2. The most prevalent OCT findings were drusen ($n = 13$, 30%) and subretinal hemorrhage ($n = 6$, 14%) (Fig. 1b-c). FA and ICGA were performed for 32 eyes (74%), and the most frequent findings were blocked fluorescence due to hemorrhage (subretinal, sub-RPE; 56%) and peripheral leakage (53%). Peripheral polypoidal lesions in ICGA and choroidal neovascularization in FA were seen in five (16%) and two (6%) eyes, respectively (Fig. 2).

In more than half of the patients (56%), the referral diagnosis was choroidal melanoma, and 25% of patients had a diagnosis of vitreous hemorrhage/opacity. Only three (8%) patients were referred with a correct diagnosis of PEHCR (Table 2). During the follow-up period, 37 (86%) of the total 43 eyes received some kind of treatment, while for six (14%) eyes, only observation was performed (Table 3). The most commonly prescribed treatment was anti-VEGF injection ($n = 29$, 67%), with an average of 3.7 injections administered. Vitrectomy was performed in 19% and 22% of patients as monotherapy or in combination with anti-VEGF injection, respectively, with the most common indications being vitreous hemorrhage ($n = 8$, 53%) and retinal detachment ($n = 3$, 21%). Concurrent intraocular lens implantation was performed in six (40%) cases.

Regarding visual outcomes, we found no significant changes in BCVA between the baseline and last follow-up visits, neither among patients who received treatment (1.11 ± 0.88 vs. 1.07 ± 0.89, $p = 0.42$) nor among those who underwent only observation (0.30 ± 0.47 vs. 0.77 ± 1.13, $p = 0.197$) (Table 1).

Discussion

The present study demonstrated that PEHCR most commonly presented at approximately 70 years (mean age, 70.1 years) and predominantly affected women (70%). Hypertension, diabetes, and systemic malignancy were identified as the most common risk factors. The majority of patients had decreased BCVA, while 26% had no ocular symptoms at the first visit. Notably, only 8% of patients were referred with a correct diagnosis of PEHCR, whereas a substantial number of patients (56%) were referred with a diagnosis of choroidal melanoma. The lesions were primarily located in the inferotemporal and superotemporal quadrants, and exudation was the most prevalent finding. Most patients received treatment, with anti-VEGF injections prescribed most frequently.

Characteristics	Value
Age, years	70.1 ± 13.2 (18–87)
Sex, n (%)	
Male	12 (33.3)
Female	24 (66.7)
Involvement, n (%)	
Bilateral	7 (19.4)
Unilateral	36 (80.6)
Follow-up duration (years)	2.9 ± 3.0 (0.2–10.7)
Time to disease diagnosis (months)	4.0 ± 8.1 (0–40)
Comorbidity, n (%)	
Hypertension	24 (66.7)
Diabetes	9 (25.0)
Systemic malignancy	8 (22.2)
History of anticoagulant/antiplatelet therapy	6 (16.7)
Ischemic heart disease	5 (13.8)
Symptoms at first visit	
Decreased visual acuity	18 (41.8)
Floaters	7 (16.2)
Visual field defect	4 (9.3)
Darkness or 'curtain'	2 (4.6)
Metamorphopsia	1 (2.3)
No ocular symptoms	11 (25.6)
Initial BCVA distribution, logMAR (Snellen)	
'≤ 0.30 (20/40)	18 (41.9)
between 0.30 and 1 (20/40 and 20/200)	10 (23.3)
> 1 (20/200)	15 (34.9)
Mean initial BCVA, logMAR (Snellen)	0.95 (20/182)
Visual acuity change analysis	
BCVA in the treatment group, logMAR (Snellen)	
First visit	1.11 ± 0.88 (20/258)
Last visit	1.07 ± 0.89 (20/235)
p-value	0.421
BCVA in the observation group, logMAR (Snellen)	
First visit	0.3 ± 0.47 (20/40)
Last visit	0.77 ± 1.13 (20/118)
p-value	0.197

Table 1. Baseline characteristics and visual acuity change analysis. Values were presented as mean ± standard deviation (range) or number (%). P-values of less than 0.05 indicates statistical significance. The Wilcoxon signed-rank test was used for nonparametric variables. Visual acuity was reported in Snellen notations and converted to logarithm of the minimum angle of resolution (logMAR) units. Visual acuity levels of counting fingers, hand motion, light perception, and no light perception were converted into 2.3, 2.6, 2.9, and 3.2 logMAR units, respectively. BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimal angle of resolution.

The age and sex distribution of PEHCR among Asian patients observed in this study was consistent with the previously reported findings in Caucasian patients of female predominance of 60–70% and a mean presentation age between 70 and 80 years[4,5]. Similarly, our results regarding systemic risk factors were consistent with those of previous studies[4,5,9,10].

Ocular symptoms were present in most of the patients (74%), while only 26% were asymptomatic. In contrast, Shields et al. reported that only 58% of patients with PEHCR developed ocular symptoms[4]. However, in other studies, the proportion of asymptomatic patients (28%) was similar to that observed in the current study[10]. Compared to Shields' study, the proportion of symptomatic cases in this study was higher, with a greater incidence of reported visual impairment and visual field defects[4]. This is likely due to the higher frequency of vitreous hemorrhage (42% vs. 14%) and macular lesions, such as submacular hemorrhage (14% vs. 5%), which are conditions more likely to be perceived by patients. At the initial visit, the mean BCVA was 0.95 logMAR (Snellen equivalent, 0.11). A relatively even distribution was identified in the three categorized groups, with patients with a BCVA of 0.30 logMAR (Snellen equivalent, 0.5) or lower accounting for the highest proportion. This is consistent with the findings of previous studies, which reported various initial BCVA distributions[4,5,10].

Findings	Value
Primary diagnosis	
Choroidal melanoma	20/43 (55.6)
Vitreous hemorrhage/opacity	7/43 (25.0)
Retinal detachment	3/43 (8.3)
PEHCR	3/43 (8.3)
Age-related macular degeneration	2/43 (5.6)
Metastatic cancer	2/43 (5.6)
Hemangioma	1/43 (2.8)
Location of PEHCR lesions	
Inferotemporal	25/43 (58.1)
Superotemporal	22/43 (51.2)
Inferonasal	3/43 (6.9)
Superonasal	2/43 (4.7)
Peripheral findings	
Exudation	28/43 (65.1)
Subretinal and subretinal pigment epithelium hemorrhage	23/43 (53.5)
Vitreous hemorrhage	18/43 (41.9)
Subretinal fluid	11/43 (25.6)
Chorioretinal atrophy	2/43 (4.7)
Retinal fibrosis	1/43 (2.3)
Macular OCT findings	
Drusen	13/43 (30.2)
Subretinal hemorrhage	6/43 (14.0)
Macular atrophy	2/43 (4.7)
Retinal detachment	2/43 (4.7)
Epiretinal membrane	1/43 (2.3)
FA/ICGA findings	32/43 (74.4)
Blocked fluorescence	18/32 (56.2)
Peripheral leakage	17/32 (53.1)
Peripheral polypoidal lesions	5/32 (15.6)
Macular neovascularization	2/32 (6.3)

Table 2. Primary diagnosis at the time of initial referral and associated fundus findings at presentation. Values were presented as the number of specific variables/total number of eyes (%). FA, fluorescein angiography; ICGA, indocyanine green angiography; OCT, optical coherence tomography; PEHCR, peripheral exudative hemorrhagic chorioretinopathy.

With regard to examination findings, the high prevalence of lesions in the inferotemporal (58%) and superotemporal (51%) regions we observed is consistent with previously reported results of most frequent lesion distribution in the temporal, specifically, inferotemporal quadrant[3,4]. Consistency with previous studies was also noted in terms of peripheral retinal findings, including exudation, subretinal and sub-RPE hemorrhage, and vitreous hemorrhage; FA and ICGA findings of blocked fluorescence related to hemorrhage and peripheral leakage; and macular OCT findings. Compared to Choi's previous study on an Asian population, the lesion location in this study was also predominantly in the temporal region, with common fundus findings of exudation, subretinal hemorrhage, and vitreous hemorrhage[11]. In the present study, the percentage of peripheral polypoidal lesions was 16%, while that of active CNV was 6%. When compared to the proportions reported in Choi's study (24% and 7%, respectively), the differences observed between the two studies were not significant. These findings suggest that there may be little difference in the clinical presentation of PEHCR among Asian populations. In our study, the most common OCT finding was drusen, which corresponds with the results of Choi et al., who reported bilateral choroidal thinning and drusen deposit accumulation in the macula in their patients[12]. This suggests that the pathophysiology of PEHCR can be considered a part of the age-related macular degeneration spectrum.

The pathophysiology of PEHCR is still not fully understood. Initially, based on clinical features and similarities in demographic populations, it was considered a peripheral variant of age-related macular degeneration (AMD)[13]. However, FA and pathological examination of enucleated eyes with PEHCR identified a choroidal vascular network in just a few cases[14]. Subsequent findings of abnormal choroidal vascular networks and polyp-like telangiectasias on ICGA have raised the possibility that PEHCR may be associated with polypoidal choroidal vasculopathy (PCV)[9,15,16]. In our study, peripheral polypoidal lesions and choroidal neovascularization were identified on ICGA in only 16% and 6% of cases, respectively. These findings suggest that PEHCR may share

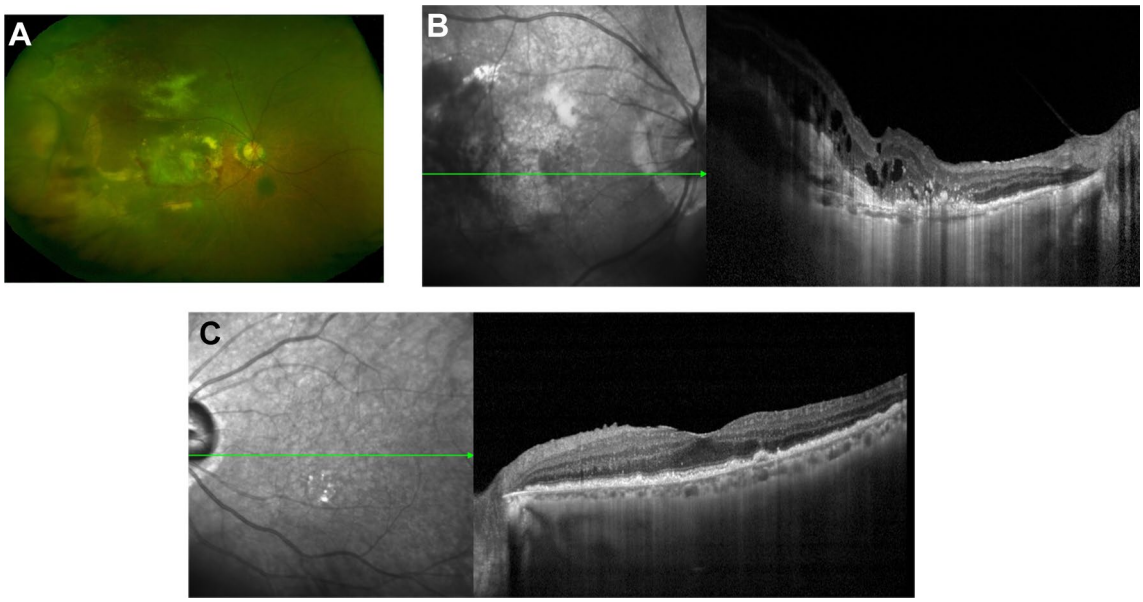

Fig. 1. Representative fundus and optical coherence tomography images. (**a**) Fundus photograph showing exudations and subretinal hemorrhages located mostly in the temporal peripheral area with macular invasion. (**b**) Optical coherence tomography image showing subretinal hemorrhages with exudations in the macula area. (**c**) Optical coherence tomography image showing drusen around the macula area without macular invasion of peripheral exudative hemorrhagic chorioretinopathy lesions.

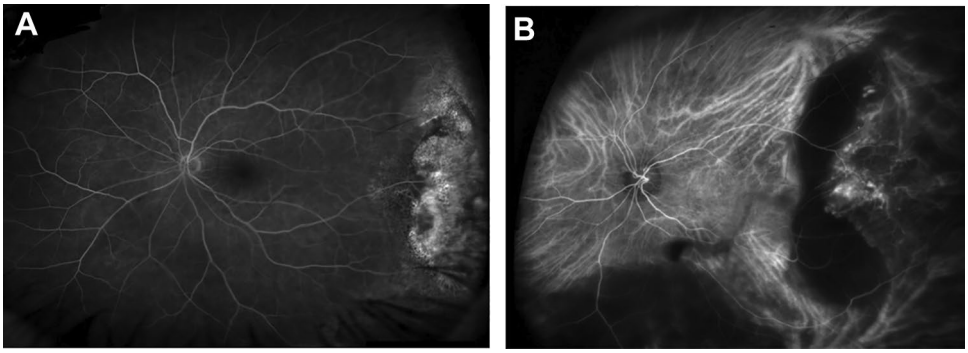

Fig. 2. Representative fluorescein angiography and indocyanine green angiography images. (**a**) Fluorescein angiography image showing peripheral leakage in the temporal area. (**b**) Indocyanine green angiography image showing blocked fluorescence and polypoidal lesions in the temporal peripheral area.

certain characteristics of both AMD and PCV, raising the possibility that it could represent a distinct, independent entity. Further investigation is necessary to clarify this possibility.

Owing to the diverse clinical manifestations and peripheral retinal locations, PEHCR has often been misdiagnosed. In the current study, more than half of the patients were referred under the diagnosis of choroidal melanoma (56%), which is consistent with previously reported observations that 23–99% of patients had an initial diagnosis of choroidal melanoma[4,5,10]. This finding emphasizes the need for careful differentiation between these two conditions because choroidal melanoma has very different prognostic implications, and patients may receive unnecessary aggressive treatments, such as enucleation or radiation[17]. Therefore, in older patients with hemorrhagic and exudative subretinal masses, PEHCR should be considered as a differential diagnosis.

The key clinical features that differentiate PEHCR from other ocular conditions are summarized as follows. Choroidal melanoma, one of the most frequently misdiagnosed entities, is a true neoplasm typically located in the posterior pole or mid-periphery. It presents as a dome- or mushroom-shaped elevation with well-defined margins and a brown to dark brown color due to abundant melanin pigmentation. The presence of lipofuscin (orange pigment) is a helpful distinguishing feature. Diagnosis requires multimodal imaging, including B-scan ultrasonography, OCT, and FA/ICGA. Metastatic choroidal tumors also commonly involve the posterior pole or mid-periphery and appear as creamy-white to yellow-gray lesions with ill-defined borders. A history of systemic malignancy is a critical diagnostic clue. These lesions are often multiple and may be bilateral, in contrast to the typically unilateral presentation of PEHCR. Choroidal hemangiomas usually occur in the

Types of treatment	Value
With treatment	37/43 (86.0)
Anti-VEGF only	21/37 (56.8)
Vitrectomy only	7/37 (18.9)
Anti-VEGF + vitrectomy	8/37 (21.6)
Transpupillary thermotherapy	1/37 (2.7)
Observation	6/43 (14.0)
Average number of injections	
Anti-VEGF + vitrectomy	3.6 ± 2.3
Anti-VEGF only	3.8 ± 2.1
Vitrectomy cause	
Vitreous hemorrhage	8/15 (53.3)
Retinal detachment	3/15 (21.4)
Biopsy	1/15 (6.7)
Others	3/15 (20.0)
Tamponade (Oil/Gas)	
Oil	4/15 (26.7)
Gas	0/15 (0.0)
Intraocular lens implantation	6/15 (40.0)
Scleral encircling	0/15 (0.0)

Table 3. Analysis of treatment in patients with PEHCR. Values were presented as the number of specific variables/total number (%) or mean ± standard deviation. PEHCR, peripheral exudative hemorrhagic chorioretinopathy; VEGF, vascular endothelial growth factor.

posterior pole and exhibit a homogenous bright reddish-orange coloration. Hemorrhage is uncommon, with exudative changes being predominant. A dome-shaped mass and the characteristic 'washout' pattern on ICGA are key distinguishing features. Finally, AMD involves the central macula and is characterized by central visual disturbances and progressive vision loss. Hemorrhage, when present, is generally confined to the central area, unlike the often extensive peripheral hemorrhage seen in PEHCR.

PEHCR lesions commonly stabilize or regress spontaneously in the majority of cases; thus, patients usually require only observation[4]. The use of anti-VEGF may be advocated when subfoveal extension with subretinal fluid or hemorrhage occurs, and vitrectomy can be considered to treat long-standing uncleared vitreous hemorrhage or retinal detachment[18]. In our study, 86% of patients received some form of treatment, with the most common being intravitreal anti-VEGF injections, while 14% of patients received no treatment. Among the 21 eyes that received intravitreal anti-VEGF injections, 20 (95%) were treated with bevacizumab, and 1 (5%) was treated with aflibercept. Improvement in visual acuity or regression of peripheral and macular lesions was observed in 15 eyes (71%). In cases without improvement in vision or lesion status, this may be due to progression to hemorrhagic retinal detachment requiring vitrectomy, presence of macular atrophy, or insufficient follow-up duration.

In the analysis of BCVA changes according to the treatment approach, although the initial BCVA was significantly better in the observation group than in the treatment group, we found no statistically significant BCVA changes between the initial and final visits in either group. In the treatment group, although some improvement in BCVA was observed, the changes between the initial and last visits were not statistically significant despite treatment. This is probably owing to the fact that some patients may have had already progressed lesions, such as hemorrhagic retinal detachment with poor BCVA at the initial visit, and some cases were refractory to treatment, with progression of the subretinal hemorrhage despite treatment. These results are consistent with previously reported findings that the majority of asymptomatic patients required only observation, and management, such as anti-VEGF or vitrectomy, may be warranted for cases of progressive lesions or non-clearing vitreous hemorrhage[4,5,10].

In recent years, various treatment methods have been attempted in patients with PEHCR, including intravitreal bevacizumab, photocoagulation, cryotherapy, and combined treatments. In a study by Takkar et al., PEHCR with macular involvement was treated with combination therapy involving anti-VEGF and laser photocoagulation of extrafoveal choroidal neovascularization lesions, resulting in the resolution of the subretinal fluid and stabilization of extrafoveal choroidal neovascularization[19]. Thus, various treatment methods should be considered for refractory PEHCR cases.

The major strength of this study is the relatively large number of enrolled patients considering the low prevalence of PEHCR in the Asian population. Although the inherent limitations of the retrospective design cannot be ignored, we believe that the findings of this study make a good foundation for future research on PEHCR in Asian patients and will be useful as a diagnostic reference for PEHCR.

In conclusion, PEHCR is an uncommon degenerative condition with diverse presentations in the peripheral retina, including massive subretinal or intraretinal hemorrhages with exudates and subretinal fluid. For these reasons, patients with PEHCR are often misdiagnosed and are at a high risk of delayed diagnosis and

inappropriate treatment. Therefore, these patients require careful monitoring and optimized management to reduce the risk of vision-threatening complications.

Data availability

All data used during this study are included in this published article. Additional datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions

H.L. conceptualized and designed the study, collected and analyzed the data, drafted and wrote the initial manuscript, and critically reviewed and revised the manuscript. Y.J.C. and S.M.L. conceptualized and designed the study, collected the data. J.L. and E.Y.C. critically reviewed the manuscript. M.K. conceptualized and designed the study, collected and analyzed the data, drafted the initial manuscript, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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