Updated Systematic Review and Clinical Spectrum of Peripheral Exudative Hemorrhagic Chorioretinopathy

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Abstract:
Peripheral exudative hemorrhagic chorioretinopathy (PEHCR) is a rare retinal vasculopathy that might cause subretinal and/or vitreous hemorrhages. Although the primary etiology is still unknown, choroidal neovascularization is mainly involved in the pathogenesis. The main risk factors are age and systemic hypertension. Ancillary testing such as fluorescein angiography, indocyanine green angiography and ultrasonography can be of great value for diagnosing this entity and distinguishing PEHCR from other lesions as choroidal melanoma and retinal vasoproliferative tumor. Various treatments have been reported including photoagulation, cryotherapy, intravitreal injection of anti-vascular endothelial growth factor (Anti-VEGF) and surgical intervention as pars plana vitrectomy. This review handles an up-to-date perspective regarding PEHCR.

Keywords:
Antivascular endothelial growth factor, choroidal neovascularization, peripheral exudative hemorrhagic chorioretinopathy, photoagulation, pseudomelanoma

Introduction

Peripheral exudative hemorrhagic chorioretinopathy (PEHCR) is a medical term used to describe a clinical entity occurring in the peripheral retina, similar to age-related macular degeneration (ARMD). It has many different synonyms including, eccentric disciform degeneration, peripheral disciform degeneration, in addition to a peripheral hemorrhagic detachment of the retinal pigment epithelium (RPE).[1]

In 1961, Reese and Jones were the first to describe that condition when they detected chorioretinal lesions that were similar to ARMD lesions. However, they were uncharacteristically located outside the macular region.[2]

In 1980, Annesley et al. termed these lesions as “PEHCR.”[3] Mashayekhi et al. reported that this condition was characterized by an extramacular hemorrhage in the subretinal or sub-RPE region, along with a peripheral exudative mass.[4] Affected eyes can also show severe lipid exudate around the blood vessels.[5] Although affected patients are frequently asymptomatic and have a good outcome, vitreous hemorrhage (VH) and/or subretinal hemorrhage with macular involvement can impair vision.[6]

PEHCR is not well known due to its low frequency, difficulty to diagnose and non-standardization of its clinical entity.[7] Moreover, PEHCR can appear to simulate choroidal melanoma (pseudomelanoma) which may lead to enucleation in some cases. Among simulating lesions, it was previously reported that PEHCR occupied the second most frequent condition after...
choroidal nevus in the assessment of melanoma-like lesions.\textsuperscript{[9]}

Bilateral lesions are found in 18\%–37\% of cases. These lesions are commonly located in the mid-peripheral or peripheral regions, especially the inferior temporal quadrant.\textsuperscript{[9]} The diagnosis of PEHCR appears to be mostly clinical, based on careful examination of the retinal fundus.\textsuperscript{[10,11]}

### Risk Factors

PEHCR is commonly diagnosed in older populations, similar to its counterpart, ARMD.\textsuperscript{[8]} In 2009, Shields et al. reported that the average age of cases was 80 years.\textsuperscript{[1]} Additionally, Mantel et al. recommended excluding PEHCR for patients under the age of 60.\textsuperscript{[12]}

Females usually have a high predominance in having this condition when compared to males. One study reported that 68.9\% of the included cases were females.\textsuperscript{[12]} Multiple published articles have also confirmed this finding.\textsuperscript{[7,13,14]} This could be explained by the fact that females usually have higher life expectancy compared to males, making them more likely to reach the age when the disease becomes symptomatic.\textsuperscript{[12]}

Systemic hypertension and age have been reported to be a risk factor for both PEHCR and ARMD.\textsuperscript{[7]} Kim et al. found that hypertension was present in 75\% of their included cases.\textsuperscript{[13]}

Anticoagulant intake has also been linked as a risk factor for PEHCR. It is well known that such medications increase bleeding tendencies.\textsuperscript{[1,16]} Vandefonteyne et al. noticed that 35.7\% and 8.9\% of the included cases were receiving platelet aggregation inhibitors and anticoagulants, respectively.\textsuperscript{[10]}

The reported incidence of ARMD ranges between 4.5\% and 39\% in cases with PEHCR\textsuperscript{[3,10]} and even up to 68.9\% according to Mantel et al.\textsuperscript{[12]} Although ARMD and PEHCR share some clinical features and age distribution, they are separate clinical entities as PEHCR could exist without ARMD. Additionally, Drusen, which are the hallmark of ARMD, could not be detected in PEHCR cases.\textsuperscript{[7]} Nevertheless, many ophthalmologists consider PEHCR a variant of ARMD.\textsuperscript{[17]}

About 99\% of PEHCR cases were in Caucasians,\textsuperscript{[7]} a predilection for the White race has been confirmed by two other large series.\textsuperscript{[12,18]} PEHCR is extremely uncommon in Asians and only three isolated cases have been reported among Indians.\textsuperscript{[19–21]} Therefore, the Caucasian race may be considered an inherent risk factor for having this condition.

### Etiology

Although the exact etiology remains unknown, peripheral neovascularization has been suggested.\textsuperscript{[22]} The similarities between the clinical course and fundoscopic features between PEHCR and polypoidal choroidal vasculopathy (PCV) support that hypothesis.\textsuperscript{[4]} However, neovascularization could not be demonstrated on histological examination, with only RPE rupture that was evident and through to be responsible for the retinal hemorrhage.\textsuperscript{[12]}

### Clinical Features

Visual loss is the most common complaint, followed by floaters and flashes. Patients may experience metamorphopsia, scotoma, visual field defects and pain.\textsuperscript{[10]} Pain could be explained by angle closure that results from massive peripheral hemorrhage.\textsuperscript{[22]}

Shields et al. reported that most PEHCR cases were asymptomatic (about 89\%); therefore, conservative treatment should be the first choice in their management.\textsuperscript{[7]}

### Fundus examination and photography

Findings include VH, subretinal hemorrhage, sub-RPE hemorrhage, RPE tear, detachment, or subretinal fibrosis [Figure 1]. Moreover, lipid exudation [Figure 1] might be encountered. Some features may indicate chronicity such as RPE hyperplasia or atrophy [Figure 1], which means that there were previously undocumented lesions.\textsuperscript{[7,9,20]} Ultra-wide-field imaging helps in diagnosis and monitoring the course of the disease, as the pathology frequently lies anterior to the equator.\textsuperscript{[20]}

### Optical Coherence Tomography (OCT)

Macular OCT can give an accurate measurement of the extent of subretinal hemorrhage or fluid into the foveal region. When visual impairment is reported, it is recommended to perform an OCT\textsuperscript{[24]} [Figure 2].

### Ultrasound (US)

B-scan (US) typically reveals the presence of a dome- or plateau-shaped mass with a hollow acoustic quality. US can detect absent choroidal excavation, absent vascular pulsation, and presence of clot retraction cleft [Figure 3], which are important features seen in PEHCR.\textsuperscript{[7]}

As regards the internal reflectivity, no classic features have been determined yet, as internal reflectivity may be low, intermediate, or high (41, 36, and 19\%, respectively).\textsuperscript{[7]}

Retinal vasoproliferative tumors (VPTs) tend to show medium-to-high internal reflectivity on A-scan and retinal solid lesion without choroidal excavation on B-scan.\textsuperscript{[25]}
Fluorescein Angiography (FA)

FA may show choroidal blockage due to subretinal hemorrhage, sub-RPE hemorrhage, or RPE hyperplasia. In addition, peripheral hyperfluorescence and window defect patterns might be seen due to RPE atrophy. While choroidal neovascularization is rarely encountered in these cases, an abnormal choroidal network can be detected.

Other non-significant findings include abnormal retinal circulation, hemi-central vein occlusion and delayed retinal filling.

Indocyanine Green (ICG) Angiography

Mantel et al. reported in two studies that ICG angiographic findings include pathological choroidal vascular polyps resembling PCV [Figure 4]. The presence of a giant RPE rip most evidenced on ICG supports the hypothesis of PEHCR being a peripheral variant of PCV as proposed.

Differential Diagnosis

The most important differential diagnosis that should be considered is choroidal melanoma. To distinguish it from PEHCR, US and FA are useful tools. PEHCR and melanoma share the choroidal blockage feature due to subretinal hemorrhage in PEHCR and RPE proliferation in melanoma; choroidal melanomas show intrinsic vascularity with double circulation on FA. B-scan US shows fluid or blood in the subretinal or sub-RPE regions in PEHCR. Unlike choroidal melanoma, no choroidal excavation is seen on B-scan.

Furthermore, PEHCR is usually located at the periphery, while melanoma occurs between the macula and the equator. Melanoma involves less than one quadrant, but PEHCR usually affects more than one quadrant.

VPT can mimic PEHCR as they share some characteristic features, including the high possibility to involve the peripheral fundus, presence of VH, subretinal hemorrhages, exudation and RPE changes. The most useful modality to differentiate between both entities is FA, which shows early hyperfluorescence with late leakage at the level of the retina, commonly seen with VPT.

Table 1 summarizes the different features among the three mentioned diseases.
Prognosis

About 90% of PEHCR lesions resolve spontaneously, leaving an area of RPE atrophy, hyperplasia, or fibrosis. Progression to the foveal region is only detected in 11% of cases.\cite{Kim}

Kim et al. reported that there is a greater tendency for subfoveal extension in the Asian population, but the different disease natures between Asian and Caucasian populations were not well established.\cite{Badawi}

Generally, PEHCR has a favorable prognosis; nevertheless, the lesion may become enlarged due to recurrent hemorrhage, leading to visual impairment.\cite{Badawi}

Treatment

Multiple modalities are existing for managing PEHCR, including; laser photocoagulation, cryotherapy, photodynamic therapy (PDT), and intravitreal injection of anti-vascular endothelial growth factor (Anti-VEGF), such as Bevacizumab and Ranibizumab.\cite{Badawi}

The first two modalities are always useful if peripheral vascular nets are detected.\cite{Badawi} However, their efficacy in other conditions is a matter of debate. Subretinal hemorrhage could be exaggerated by laser therapy and could cause cystoid macular edema development, while cryotherapy may induce subretinal fibrosis.\cite{Badawi}

PDT using Verteporfin could be helpful in the presence of subfoveal choroidal neovascularization, but choroidal atrophy may worsen after treatment.\cite{Badawi}

Previous reports indicated that intravitreal Bevacizumab monthly injections resulted in good visual improvement and resolution of pre-existing subretinal hemorrhages, with stable lesion size.\cite{Badawi,Badawi} Similar therapeutic effects were reported using monthly Ranibizumab injections.\cite{Badawi} Favorable anatomical and functional outcomes were also reported with monthly intravitreal Aflibercept injections.\cite{Badawi} In a recent study, intravitreal Anti-VEGF injections were used in 51 out of 89 eyes with PEHCR and found limited visual improvements. This might be explained by the late initiation of injection.\cite{Badawi}

### Table 1: Summarizes the different features among common differentials diagnosis

| Origin of the lesion | Chorioretinal | Choroidal | Retinal |
|----------------------|---------------|-----------|---------|
| PEHCR                | Mostly solitary choroidal pigmented mass, located from the macula up to the equator | Signs: Brown Choroidal mass with overlying orange pigments, Dome shaped 75%, mushroom shaped configuration 20%, Exudative RD, Drusen | Signs: Pinkish or yellowish in color at the retinal surface, Telangiectatic vessels and small aneurysms over the lesion, Extensive exudates around lesion, Exudative retinal detachment, Slight enlargement of retinal feeder vessels, Epiretinal enlargement of retinal detachment |
| Choroidal             | Subretinal Hg | Subretinal pinpoint hyperfluorescence (hot spots), Blockage effect due to the choroidal mass, Positive double circulation pattern | Globular in shape, located in the peripheral retina commonly (Inferior temporal) |
| Retinal              | Sub RPE Hg    | Subretinal pinpoint hyperfluorescence (hot spots), Blockage effect due to the choroidal mass, Positive double circulation pattern | Unilateral |
| Lipid exudation       | Lipid exudation | Lipid exudation | Unilateral |
| Vitreous Hg           | Vitreous Hg | Vitreous Hg | Unilateral |
| RPE hyperplasia and atrophy peripherally indicate: chronicity | Vitreous Hg can be seen rarely |

Laterality

Mostly unilateral 67% | Unilateral | Mostly unilateral |
Bilateral 33%  |

FFA findings

By subretinal hemorrhage | Early hyperfluorescence with late leakage and staining, Subretinal pinpoint hyperfluorescence (hot spots) | Early hyperfluorescence with late leakage at the level of the retina |
Peripheral hyperfluorescence due to RPE atrophy (window defect) | Subretinal pinpoint hyperfluorescence (hot spots) | Telangiectatic vessels on the surface of the lesion |
Negative double circulation pattern | Blockage effect due to the choroidal mass, Positive double circulation pattern | Negative double circulation pattern |

B-scan

Dome or plateau-shaped mass | Mushroom- or dome-shaped mass, Presence of choroidal excavation and orbital shadowing | Solid mass |
Absence of choroidal excavation and orbital shadowing | Presence of choroidal excavation and orbital shadowing | Absence of choroidal excavation and orbital shadowing |
Presence of retraction cleft | Absence of retraction cleft |

A-scan

Variable | Low to medium internal reflectivity | Medium-to-high internal reflectivity |

Hg: Hemorrhage, RPE: Retinal Pigmented Epithelium, RD: Retinal Detachment
Furthermore, the use of laser photocoagulation, in combination with Anti-VEGF, has been advocated as the treatment of choice for choroidal neovascular membrane associated with subretinal fluid in the macular region.[21]

Less commonly, surgical intervention may be necessary to treat massive submacular hemorrhage and/or VH.[16,33] One series included five cases of dense VH, which required pars plana vitrectomy.[6] The authors reported that optimal visual and anatomic results could be obtained with PPV to clear the hemorrhage and additional treatment may not be needed, even at long-term follow-up.[6]

Conclusion

PEHCR is a rare retinal vasculopathy disorder presumed to be associated with aging and systemic hypertension. It is usually asymptomatic but can cause a decrease in vision. Ancillary retinal testing, including FA, ICG, and ultrasonography, can be of great value for diagnosing this entity and distinguishing PEHCR from other lesions as choroidal melanoma and retinal vasoproliferative tumor. Most lesions are usually observed. Treatment modalities include Anti-VEGF, photocoagulation, PDT, and cryotherapy. Surgical intervention is reserved for unresolved VH and/or subretinal hemorrhage involving the macula as these presentations are the most prevalent causes of a decline in vision. Subsequent follow-up visits are recommended in asymptomatic patients for possible complications, which might affect sight.

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Conflicts of interest

There are no conflicts of interest.

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