EVEREST study report 3: diagnostic challenges of polypoidal choroidal vasculopathy. Lessons learnt from screening failures in the EVEREST study

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Abstract
Purpose To describe screening failures in the EVEREST study by examining the imaging characteristics that enabled differentiation of polypoidal choroidal vasculopathy (PCV) from cases that were subsequently diagnosed not to be PCV.
Methods Post-hoc analysis of 34 patients with PCV reported as screening failures from EVEREST study. Standardised confocal scanning laser indocyanine green angiography (ICGA) images were graded by the Central Reading Centre to confirm PCV diagnosis based on the presence of early focal sub-retinal hyperfluorescence on ICGA and at least one of the following six diagnostic criteria: (1) nodular appearance of polyp(s) on stereoscopic examination, (2) hypofluorescent halo around nodule(s), (3) presence of a branching vascular network, (4) pulsation of polyp(s) on dynamic ICGA, (5) orange sub-retinal nodules on colour fundus photography, or (6) massive sub-macular haemorrhage (≥4 disc areas in size). Additional detailed image grading was performed with stereo-imaging and dynamic early-phase ICGA.
Results Of the 95 screened PCV cases, 34 were excluded: (1) cases not suitable for recruitment as per the study protocol (n=14), (2) equivocal lesions on ICGA characterised by small hyperfluorescent dots (n=9), and (3) cases that were definitely not PCV (non-PCV, n=11), identified by definitive diagnoses which included one case each of micro-aneurysm, retinal angiomatous proliferation, retino-choroidal anastomosis, small type-2 choroidal neovascularisation, retinal pigment epithelial (RPE) window defect and disciform scar; two cases of lesions where the choroidal vessel changed its course; and three cases of late-onset RPE staining.
Conclusions Standardised image grading techniques used in EVEREST study enabled effective differentiation of non-PCV from actual PCV.

Keywords EVEREST study · Polypoidal choroidal vasculopathy · Indocyanine green angiography · non-PCV · Age-related macular degeneration

Introduction
Polypoidal choroidal vasculopathy (PCV) is generally considered a subtype of neovascular age-related macular degeneration (nAMD), a variant of Type 1 choroidal neovascularisation (CNV). However, some investigators believe that PCV is a discrete vascular abnormality of the choroidal vessels [1, 2]. PCV mostly affects patients aged 50 to 65 years [3] and accounts for up to 23.9–54.7 % of presumed nAMD in Asian populations [4–8] and about 8–13 % in Caucasians [9].

The understanding of PCV has evolved considerably over the past few decades [10]. The natural course of PCV has been shown to be favourable compared to typical nAMD, with up to 50 % of patients showing spontaneous resolution of presenting features [11]. However, some patients with PCV may have repeated episodes of haemorrhage and leakage, resulting in significant loss of vision [7, 11, 12]. Typical presentation of eyes with PCV includes serosanguineous maculopathy,
This page contains a detailed discussion on the differentiation of conditions that may masquerade as PCV. The text explains that misdiagnosis of typical nAMD or other choroidal diseases as PCV can lead to inappropriate treatment and highlights the importance of accurate identification and differentiation of PCV. It notes that the EVEREST study was the first ICGA-guided, phase IV, multicentre, randomised clinical trial on PCV treatment. The study design and outcomes are described, emphasizing the need for definitive diagnosis and accurate identification of PCV.

The methods section outlines the phase IV, multicenter, exploratory study, which assessed the visual outcomes of patients treated with verteporfin photodynamic therapy compared to typical nAMD. It mentions the EVEREST study, highlighting its importance in randomised clinical trials for PCV.

The text also discusses the angiographic findings of the non-PCV cases in the EVEREST study and the differentiating features. It concludes by reiterating the importance of accurate diagnosis and management of PCV to prevent inappropriate treatment.
The standardised diagnostic criteria used in the EVEREST study to confirm PCV diagnosis consisted of the presence of early sub-retinal focal hyperfluorescence on ICGA (within the first 6 min), and at least one of the following criteria: (1) nodular appearance of the polyp(s) on stereoscopic examination, (2) hypofluorescent halo around the nodule(s), (3) presence of a BVN, (4) pulsation of the polyp(s) on dynamic ICGA, (5) orange sub-retinal nodules on colour fundus photography that correspond to the ICGA nodules, or (6) massive sub-macular haemorrhage (≥4 disc areas in size). Angiograms of all the patients were further graded by trained retinal specialists at the CRC (CST and THL) in order to identify the features which differentiated PCV from non-PCV cases. Lesion size was determined by using a best-fit circle which was drawn around each polyp using the proprietary Heidelberg Eye Explorer software, as previously described. [13] The diameter of this circle was taken as the diameter of the polyp.

**Statistical analysis**

Statistical analysis was performed using SPSS version 16.0 (SPSS Inc, Chicago, IL, USA), with p values <0.05 regarded as statistically significant. Continuous variables were compared using t-tests, while categorical variables were compared using the chi-square or Fisher exact test.

**Results**

Of the 95 patients screened, 61 were diagnosed with PCV by the CRC and enrolled in the EVEREST study, and the remaining 34 patients were reported as screening failures. All patients were treatment naive, and only one eye from each patient was included in this study. For patients with bilateral disease, the eye with the more severe pathology was selected.

The screening failure cases (n=34) were categorised into three groups: (1) PCV cases not suitable for recruitment because the location and/or lesion size of PCV did not meet the inclusion criteria (n=14); (2) cases with equivocal lesions on ICGA characterised by small hyperfluorescent dots (which were typically <150 μm in diameter) (n=9); and (3) cases that were definitely not PCV or ‘non-PCV’ cases, where a positive differential diagnosis was made (n=11). There were no significant differences in age, sex, or laterality among patients with confirmed PCV and those with non-PCV.

The 11 cases that were identified as non-PCV included one case each of micro-aneurysms, RAP, retino-choroidal anastomosis, focal CNV, RPE window defect, and disciform scar; two cases of hyperfluorescent spots located where the choroidal vessel changed its course; and three cases of late-onset RPE staining (Table 1). A selection of these cases is described below.

| Sr. No. | Age (years) | Gender | Eye (R/L) | Diagnosis | BVN | Hypofluorescent halo | Nodularity | Orange nodule | Pulsatile | Massive submacular haemorrhage |
|---------|-------------|--------|-----------|-----------|-----|--------------------|------------|---------------|-----------|-----------------------------|
| 1       | 76          | Male   | R         | Late onset RPE staining | No  | No                 | No         | No            | No        | No                          |
| 2       | 69          | Male   | L         | Late onset RPE staining | No  | No                 | No         | No            | No        | No                          |
| 3       | 66          | Male   | L         | Late onset RPE staining | Yes | No                 | No         | No            | No        | No                          |
| 4       | 67          | Male   | R         | RPE window defect | No  | No                 | No         | No            | No        | No                          |
| 5       | 84          | Male   | R         | Choroidal vascular knuckle | Yes | No                 | No         | No            | No        | No                          |
| 6       | 52          | Female | L         | Choroidal vascular knuckle | Yes | No                 | No         | No            | No        | No                          |
| 7       | 54          | Male   | R         | Micro-aneurysm | No  | No                 | No         | No            | No        | No                          |
| 8       | 18          | Female | R         | RAP | No  | No                 | Yes (intraretinal) | No         | No        | No                          |
| 9       | 62          | Male   | R         | Retinal choroidal anastomosis | Yes | No                 | Yes (intraretinal) | No         | No        | No                          |
| 10      | 69          | Female | L         | Focal CNV | No  | Yes                | No         | No            | No        | No                          |
| 11      | 76          | Male   | R         | Disciform scar | No  | No                 | No         | No            | No        | No                          |

*BVN* branching vascular network, *CNV* choroidal neovascularisation, *PCV* polypoidal choroidal vasculopathy, *R/L* right/left, *RAP* retinal angiomatosus proliferation, *RPE* retinal pigment epithelium
Cases identified as non-PCV

a) **Microaneurysms secondary to diabetic macular oedema.** This patient manifested with hard exudates and small red lesions, which may be confused with orange nodules of PCV. On ICGA, multiple small discrete round hyperfluorescent lesions were seen. Stereoscopic examination of these lesions revealed that they were superficially located, within the retinal layers. No other features of PCV, such as BVN or hypofluorescent halo, were observed. Fluorescein angiography (FA) images revealed an irregular foveal avascular zone, telangiectasia, and late leakage from these lesions, which were diagnosed as retinal microaneurysms secondary to diabetic maculopathy (Fig. 1).

b) **RAP.** In this patient, focal early hyperfluorescence was observed on the ICGA image of the study eye, which suggested the possible presence of a polyp. However, dynamic ICGA showed filling of this lesion from the retinal circulation and subsequent drainage of the dye into the retinal vein superiorly. In addition, stereoscopic examination showed that the lesion was superficial. Other features, such as BVN, pulsation, orange nodules, or massive submacular haemorrhage were not observed. FA images showed leakage and pooling within intra-retinal cystoid spaces. These findings indicated the presence of RAP in the study eye (Fig. 2).

c) **Retinal pigment epithelium window defect.** Subretinal haemorrhage surrounding a CNV lesion was seen at the macula. An area of early ICGA hyperfluorescence was noted along the inferotemporal arcade (Fig. 3). However, stereoscopic examination revealed that it was located in the choroid, beneath an area of RPE defect. Further examination of the dynamic ICGA showed that the area was continuous with the large choroidal vessel. In addition, other ICGA features typical of PCV were absent. Closer examination of the colour fundus photography revealed a corresponding area of chorioretinal atrophy. Likewise, a corresponding area of RPE window defect was noted on FA. This enhanced the visibility of the underlying choroidal vessel, which made it look brighter on ICGA.

d) **Change in course of the choroidal vessel.** This patient had subretinal haemorrhage at the edge of the macula, and examination of the ICGA showed a circular area of hyperfluorescence within the macula. However, on stereoscopic examination, it was found that the lesion was neither nodular nor raised. A closer examination of the dynamic ICGA images showed that this lesion was continuous with the underlying choroidal vessels, and occurred at a site where the choroidal vessel changed its course. The resultant increase in blood column at that point made it look brighter on ICGA.
location resulted in increased intensity of the ICGA hyperfluorescence, which appeared similar a polyp. Patchy chorioretinal atrophy was also observed at the macula, which enhanced visibility of the underlying chorioidal vessels, thus making this region look more fluorescent on the ICGA (Fig. 4).

c) **Focal RPE staining.** Focal hyperfluorescence was noted nasal to the fovea at 10 min still frame of ICGA (Fig. 5). A separate CNV lesion was noticed in the subfoveal region, non-contiguous to the late hyperfluorescence. Examination of 1-, 3-, and 5-min still frames did not show any convincing lesion at the same location. In addition, the 20-min still frame did not show “late dye hollowing”. Stereoscopic examination showed the lesion at the level of RPE. The lesion is consistent with focal RPE staining with ICG dye.

d) **Disciform scar.** Examination of the ICGA revealed an area of early hyperfluorescence along the inferotemporal arcade. However, this lesion was not nodular and did not manifest with a surrounding halo or pulsation. In addition, there was no associated BVN. FA showed staining of the disciform scar, with no active leakage at the region of the lesion. A head-on (en-face) view of the feeder vessel of the lesion emerging from the chorioidal circulation may be confused with a PCV lesion.

**Discussion**

In this study, we have described and illustrated some of the conditions that were initially diagnosed as PCV at the screening stage in the EVEREST study. A detailed assessment using the standardised imaging and grading techniques allowed the investigators to distinguish conditions such as micro-aneurysm, RAP, changes in course of the choroidal vessel and RPE staining/defect from actual PCV. These conditions are often misdiagnosed as PCV because their ICGA features manifest with hyperfluorescent lesions that appear similar to polyps on single still frames. The use of stereoscopic still frames and dynamic ICGA provided additional information such as nodularity and depth of the lesion (microaneurysms, RPE window defects), presence or absence of BVN and filling pattern (RAP).

Clinically, it is important to differentiate actual PCV from non-PCV cases to ensure that patients receive appropriate and effective treatment for their condition. For example, PCV lesions can respond well to the combination of verteporfin PDT and anti-vascular endothelial growth factor (anti-VEGF), whereas RAP and micro-aneurysms respond well to anti-VEGF monotherapy [27]. Patients with focal hyperfluorescence resulting from changes in course of the choroidal vessel, focal RPE staining, and...
no hyperfluorescent nodule; (Early ICGA demonstrating the network supplying the CNV lesion, but resultant up-regulation of VEGF production [31–34]. It is important, therefore, to distinguish PCV from non-PCV lesions, which may not require the addition of PDT to the treatment.

In a clinical trial situation, in which only patients with actual PCV may be eligible for inclusion, failure to identify patients with non-PCV at the initial presentation itself may result in some patients being recruited wrongly. This may also affect the long-term treatment outcomes and skew the study results.

Our understanding of nAMD and the wider spectrum of choroidal neovascular conditions including CNV, PCV, and RAP has increased in recent years. Advances in imaging and grading technologies have contributed to characterising these conditions accurately to aid their definitive diagnosis. Clinical experience has shown that these conditions are unique and may warrant individualised treatment for best possible outcomes [27, 35]. Data from this post-hoc analysis have shown that definitive diagnosis of PCV is possible at initial medical presentation by using ICGA together with a standardised definition for PCV diagnosis [24]. The analysis further suggests that although the presence of ICGA hyperfluorescence is the hallmark of PCV, application of diagnostic criteria, and standardised grading protocol of ICGA images are essential to prevent the misdiagnosis of polyps. ICGA has been an essential diagnostic tool for PCV for decades; however, the use of recent image grading techniques described in our analysis may help to achieve a more consistent diagnosis of PCV.

The stereo-imaging and dynamic ICGA techniques used in our analysis provided additional information for image grading and enabled differentiation of non-PCV cases from actual PCV. Stereo-imaging has been shown to assist in the differentiation of a polyp (nodular in appearance) from an RPE window defect or late RPE staining, which appears flat. By examining the location of the lesion, superficial retinal lesions such as micro-aneurysms can be differentiated from polyps, which usually occur deep beneath the RPE. In addition, the depth of the lesion and lack of nodularity is helpful in distinguishing a prominent choroidal vessel beneath an area of chorioretinal atrophy from actual polyps. Dynamic ICGA, on the other hand, can identify the difference in the pattern of blood flow between a RAP lesion and the retinal vessels.

The ICGA imaging standards, grading methods and diagnostic criteria described in the recent EVEREST study report for diagnosis of PCV can be useful in clinical practice and for future randomised controlled trials on PCV [13]. Small hyperfluorescent lesions on ICGA were excluded if these occurred in isolation (without any other diagnostic criteria of PCV) because it was difficult to determine nodularity in such small lesions. In this study, the presence of massive submacular hemorrhage with a hyperfluorescent lesion on ICGA was sufficient for the diagnosis of PCV. It was felt that a large submacular haemorrhage may mask the presence of features such as BVN, a hypofluorescent halo or the presence of an orange nodule. This decision was based on a consensus agreement of the diagnostic criteria for PCV prior to the start of this study. In addition, while submacular haemorrhages do occur in nAMD, massive macular haemorrhages are uncommon [36].

In addition to some interesting findings, our study had a few limitations. Our analysis included a small sample size. Also, we did not use optical coherence tomography (OCT) as part of the diagnostic criteria, which would have further aided in diagnosis of PCV. This study was performed in 2008, when time domain OCT was commonly used. The advent of spectral domain OCT (SD-OCT) may improve the definitive diagnosis of PCV, and is the subject of newer, ongoing studies. The patients who were diagnosed with conditions other than PCV were excluded from this prospective study.
study. As a result, it is unknown if any of these patients may have subsequently developed PCV.

In conclusion, awareness of the conditions that may mimic PCV, and their imaging characteristics, will help to reduce the possibility of misdiagnosis. Retina specialists will, therefore, be able to provide appropriate treatment to patients with true PCV, resulting in effective management of this condition. Further studies using SD-OCT, stereo-imaging, and dynamic ICGA techniques can help develop standardised criteria for the accurate diagnosis of PCV, thus enhancing patient management.

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Compliance with ethical standards

Conflict of Interest Colin S. Tan receives travel support from Bayer, Heidelberg Engineering and Novartis; Wei Kiong Ngo and Louis W. Lim have nothing to disclose; Nikolle W. Tan is on the medical advisory boards of Allergan, Bayer and Novartis. Tock Han Lim receives travel support from Heidelberg engineering and Novartis. The EVEREST study was sponsored by Novartis Pharma AG, Basel, Switzerland.

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Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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