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Polypoidal choroidal vasculopathy: an angiographic discussion

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Abstract

The understanding of polypoidal choroidal vasculopathy has evolved rapidly in the past three decades. The hallmark of the disease is the presence of typical hyperfluorescent nodules in the early phase of indocyanine green angiography. Although the classical clinical presentation is recurrent serosanguinous detachment of the retinal pigment epithelium, it may present with clinical features indistinguishable from exudative age-related macular degeneration secondary to choroidal neovascularization. Some cases may present initially with submacular haemorrhage, but later with features of exudative age-related macular degeneration. Studying the associated network of vessels using confocal scanning laser ophthalmoscopy indocyanine green dynamic angiography revealed in many cases feeder vessels, branching pattern, and leakage similar to choroidal neovascularization. Owing to the overlap of clinical and angiographic features, it may be considered as a vascular subtype of exudative age-related macular degeneration. However, having seemingly better natural history, better response to photodynamic therapy, and incomplete response to anti-vascular endothelial growth factor therapy suggests that it should be studied as a separate entity from choroidal neovascularization. Combining angio-occlusion of the polyps using photodynamic therapy and anti-permeability effect of anti-vascular endothelial growth factor therapy on the branching vascular network may provide a synergistic effect. We await the result of EVEREST trial, a multi-centre randomized controlled trial comparing photodynamic therapy, with or without ranibizumab, with ranibizumab monotherapy.

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Introduction

Polypoidal choroidal vasculopathy (PCV) is an interesting, multi-faceted disease. First described by Yannuzzi in 1980, it came to be known by various terms such as posterior uveal bleeding syndrome and multiple recurrent serosanguinous retinal pigment epithelial detachment in black women, until Yannuzzi termed it idiopathic polypoidal choroidal vasculopathy in 1990.[1] Over the next two decades, the understanding of this condition has evolved rapidly.

Clinical presentation

Although a typical case presents with recurrent acute submacular haemorrhage or serosanguinous pigment epithelial detachments (PED),[2] it is now known that many present with features similar to exudative age-related macular degeneration (AMD), namely, submacular exudation, intra-retinal thickening, serous PED,[3] fibrovascular PED, subretinal fluid collection, and disciform scar.[4] Some present with serous sensory retinal detachment, clinically indistinguishable from central serous chorioretinopathy (CSCR).[5] Still others present with patchy areas of retinal pigment epithelial (RPE) atrophy associated with intra-retinal pigmentary disturbance, often associated with visible, orange subretinal nodules (Figure 1). Rarely, PCV may present with massive spontaneous suprachoroidal haemorrhage.[6]

Although significant drusen in the affected or fellow eye is less common among PCV patients

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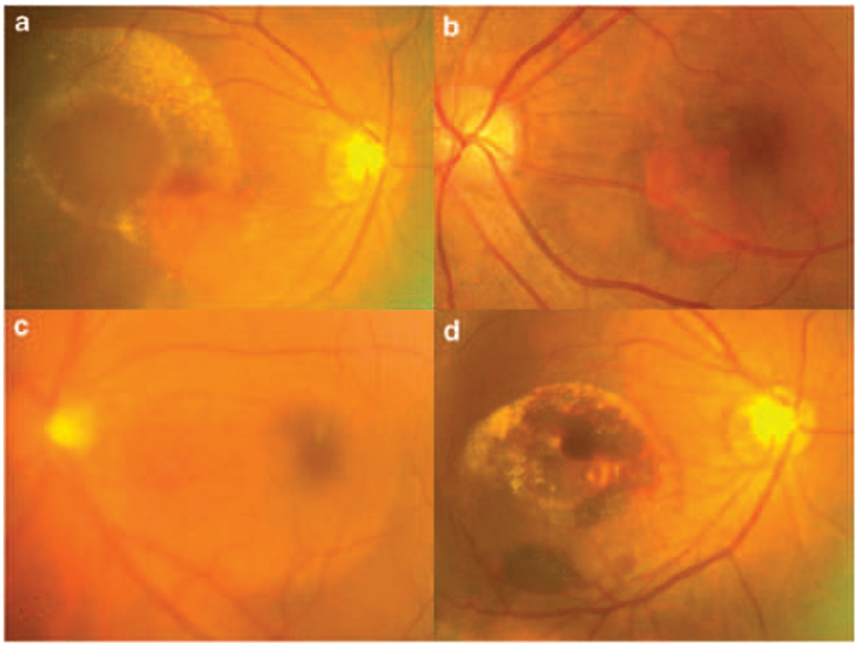

Figure 1 Various clinical presentations of PCV. (a) Massive subretinal exudation with serous pigment epithelial detachment, (b) quiescent subretinal orange nodules, (c) central serous chorioretinopathy-like presentation, and (d) serosanguinous pigment epithelial detachment.

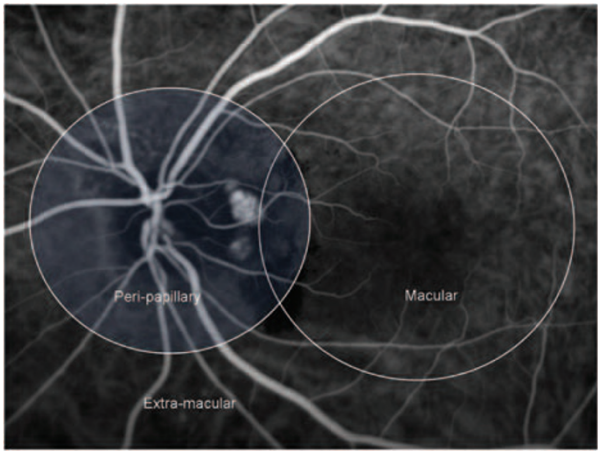

Figure 2 Classification of PCV by location.

compared to exudative AMD due to choroidal neovascularization (CNV), their presence is not uncommon, ranging from 26.7[7] to 33%.[8]

Fundus angiography

The unifying diagnostic feature in this myriad of presentations is the presence of subretinal nodular hyperfluorescence (the polyps) in fundus indocyanine green angiography (ICGA). These polyps typically appear within the first 5 min of ICGA, and persist into the late phase. In addition, at least one of the following criteria must be fulfilled to be diagnostic of PCV: (1) presence of hypofluorescent halo around the lesion, (2) presence of pulsation, (3) association with a branching vascular network (BVN), (4) correspondence to an orange-red nodule in fundus photographs, (5) a nodular appearance, rather than a flat lesion, when viewed in stereo pairs, or (6) associated with massive submacular haemorrhage (criteria from the Central Reading Centre, EVEREST trial).

The polyps may be solitary (arbitrarily defined as one or two polyps), or multiple. If multiple, the polyps may be arranged in a ring (or 'whorl' pattern) or cluster (or 'bunch of grapes'). It has been suggested that latter pattern carries a poorer prognosis.[9] A similar classification has been proposed by Cackett *et al*.[10]

Although the earlier description of a typical PCV is peri-papillary in location, it is now known that the majority of Asian cases are in the macula.[11] Although there is no unified classification system for the location of PCV, the lesion is usually described to be peri-papillary if more than half of the lesion (polyp and BVN) in ICGA is located within 1500 μm of the disc margin, and macular if more than half of the lesion is within 6000 μm diameter of the centre of fovea avascular zone excluding the peri-papillary zone. It is described to be extra-macular if more than half of the lesion is located outside the above-mentioned two zones (Figure 2). Extra-macular or peripheral PCV is uncommon, but has been reported.[12] If the lesion straddles over all the three regions, and none of the zone contains more than half of the lesion, or if

there is more than one non-contiguous lesion, it is described as 'multi-location'.

Not all focal ICG hyperfluorescences are due to PCV. Common conditions that have been misdiagnosed as PCV ('pseudo-PCV') include: stage 1 retinal angiomatous proliferation, retinal macro-aneurysm, focal RPE defect associated with a choroidal vascular knuckle. It is therefore important to study the still frames of the angiogram in stereo, and to study the earliest phase of ICGA carefully, preferably dynamically.

Fundus fluorescein angiographic (FFA) features of PCV depend on the pathological process of the disease rather than the causative vascular lesions. The majority of cases show FFA findings similar to occult CNV, typically pure occult lesions. Rarely, the polyps are visible in FFA. ICGA should be considered in patients with occult CNV,[13] particularly among patients of pigmented races.

Demography

Polypoidal choroidal vasculopathy tends to present at a younger age compared to exudative AMD.[14] The mean age of diagnosis is about 65 years, with a slight male preponderance.[15] Although initially reported among black women, recent reports have also shown that it is a common vascular subtype of exudative AMD among East Asians. PCV accounts for about $\frac{1}{4}$ to $\frac{1}{2}$ of cases manifesting as exudative AMD in Asia, compared to approximately 10% of Caucasian population (Table 1).

Pathogenesis

Although the pathogenesis of this condition is largely unknown, some anecdotal case reports point to the possible association with systemic cardiovascular risk factors, such as hypertension[16] and elevated plasma viscosity.[17]

Histopathology studies are few. Lafaut *et al*[18] found sub-RPE, intra-Bruch fibrovascular membrane with saccular aneurysmal vascular dilation. Terasaki *et al*[19] reported a specimen showing intra-Bruch dilated, thin-walled vessels without pericytes, that stained positive for vascular endothelial growth factor (VEGF) in the endothelial cells, suggesting it is neovascular in nature. Similarly, Matsuoka *et al*[20] found expression of VEGF and pigment epithelial-derived factor in both specimen of CNV and PCV, again suggesting neovascular nature of the latter condition. Likewise, Nakajima *et al*[21] reported two cases of PCV with associated CNV when examined under light microscopy.

Okubo *et al*,[22] however, reported a histopathological specimen that showed atherosclerosis of intra-choroidal arteriole, with dilation of venule at the crossing, suggesting that inner choroidal venular compression and stasis may be the causative mechanism. Likewise, Kuroiwa *et al*[23] observed changes mainly in the large choroidal arterioles, showing disruption of inner elastic layer, and deposition of basement membrane-like material and collagen in the vessel wall, suggesting that atherosclerosis of inner choroidal arterioles may be important. Similarly, Nakashizuka *et al*[24] reported hyalinization of choroidal vasculature, again underpinning the role of atherosclerosis in PCV. In the same study, however, they found no VEGF staining of the vascular endothelium of the polyps, in contrast to previous reports.

In addition, Sasahara *et al*[25] found that choroidal hyperpermeability, a common ICGA finding of CSCR, occurred in 10% of a case series of PCV. As PCV may also present as CSCR, the causative relationship between choroidal hyperpermeability, CSCR, and PCV is currently unclear.

Natural history

There is paucity in natural history data of PCV. Clinical experience suggests that PCV carries a better prognosis than exudative AMD due to CNV. Uyama *et al*[9] reported a case series of 14 eyes of 12 patients with ICG-proven PCV. Half of the patients presenting with initial VA of 20/32 or better maintained their vision without

Table 1 Proportion of PCV among eyes with exudative AMD in Caucasian and Asian population

Authors	*Population*	*No. of eyes/patients*	*PCV (%)*
Yannuzzi *et al*[14]	Americans	167 patients	7.8
Lafaut *et al*[18]	Belgians	374 eyes	12
Scassellati-Sforzolini *et al*[7]	Italians	194 patients	9.8
Ladas *et al*.[48] *Eye* 2004 May; **18**(5): 455–9	Greeks	268 patients	8.2
Wen *et al*.[49] *Graefes Arch Clin Exp Ophthalmol* 2004 Aug; **242**(8): 625–9	Chinese	166 patients	22.3
Maruko *et al*.[50] *Am J Ophthalmol* 2007 July; **144**(1): 15–22	Japanese	289 patients	55
Liu *et al*.[51] *Graefes Arch Clin Exp Ophthalmol* 2007 Oct; **245**(10): 1441–5.	Chinese	155 patients	24.5
Byeon *et al*.[52] *Jpn J Ophthalmol* 2008 Jan-Feb; **52**(1): 57–62	Korean	392 eyes	24.6

treatment, despite episodes of recurrent submacular haemorrhage. For the other half with poorer presenting VA, about 70% avoided moderate visual loss with follow-up durations of 3–5 years. Sho *et al*,[26] in a cross-sectional study of 418 eyes of presumed exudative AMD, found that 35% of PCV, as compared with 53% of exudative AMD, was associated with significantly reduced vision of 20/100 or worse.

Treatment

Polypoidal choroidal vasculopathy responds very well to angio-occlusive therapy using verteporfin photodynamic therapy (PDT). More than 15 interventional case series of verteporfin PDT for PCV had been published. Selected studies are summarized and presented in Table 2. Most studies quoted 1-year avoidance of moderate visual loss of more than 80% and three-line visual improvement of 25–55%. The response of PCV to PDT is significantly better than CNV in both visual acuity[27] and electrophysiology outcome,[28] especially among cases presenting with serous PED.[29]

However, clinical experience suggests that a subgroup of PCV patients respond poorly to verteporfin PDT monotherapy. Persistent or recurrent macular oedema is known to occur despite successful occlusion of all visible polyps. These cases were initially thought to be due to secondary CNV. Combining FFA, dynamic ICGA, and optical coherence tomographic (OCT) studies of such cases suggests that most cases are due to leakage from persistent BVN, with or without vascular remodeling, as evident by the constant location of the feeder vessel in-growth site before and after PDT (Figure 3).

Focal thermal ablation of polyps using ICGA-guided laser photocoagulation is a treatment option for PCV. However, current reports showed conflicting outcomes. Lee showed that visual stabilization can be achieved in 75% of cases treated by this modality. Yuzawa *et al*[30] reported that treating the whole lesion (polyps and network vessels) seemed to produce better results than treating the polyps alone. In the latter, more than half (54%) experienced decreased visual acuity due to persistent or recurrent leakage, presumably due to untreated vascular network. In a non-randomized comparative study, Kwok *et al*[15] found that cases treated with thermal laser photocoagulation to the polyps showed a trend of better visual outcome compared with untreated cases, though the difference was not statistically significant. Vilaplana *et al*,[31] however, reported poor visual outcome in a small case series. In the authors' opinion, ICGA-guided focal thermal ablation of polyps should be reserved for milder cases with inactive vascular network.

Branching vascular network of PCV

Although the diagnosis of PCV focuses our attention on the polyps, the authors believe that studying the associated vascular network may explain the behaviour and response to treatment of these lesions. The vascular network was termed BVN by Spaide *et al*.[32]

Branching vascular network typically persists after PDT, even when the polyps showed complete

Table 2 Results of PDT for PCV: various interventional case series

Author	N *(Eyes)*	*Duration (months)*	*Vision outcomes*
Chan *et al*.[53] *Ophthalmology* 2004; **111**: 1576–1584.	21	12	Avoid moderate visual loss (MVL) 95% Significant visual gain (⩾3 lines) 45%
Silva *et al*.[54] *Graefes Arch Clin Exp Ophthalmol* 2005; **243**: 973–979.	40	12	At 12 months, avoid MVL 82% Significant visual gain 55%
		24	At 24 months, VA improved in 5 of 6 eyes
Mauget-Faysse *et al*.[55] *Eur J Ophthalmol* 2006; **16**: 695–704.	31	12	Mean logMAR VA improved 6 letters
Akaza *et al*.[56] *Jpn J Ophthalmol* 2007; **51**: 270–277.	35	12	Avoid MVL 80%
Eandi *et al*.[57] *Retina* 2007; **27**: 825–831.	30	12	Avoid MVL 80% Significant visual gain (⩾3 lines) 50%
Otani *et al*.[58] *Am J Ophthalmol* 2007; **144**: 7–14.	47	12	Avoid MVL 87% Mean logMAR VA improved 6 letters
Gomi *et al*.[59] *Ophthalmology* 2008; 115: 141–46.	93	12	Avoid MVL 92% Significant visual gain (⩾3 lines) 25% Mean logMAR VA improved 8 letters
Kurashige *et al*.[60] *Am J Ophthalmol* 2008; **146**(4): 513–519.	41	12	At month 12, mean logMAR VA improved 4.5 letters
		24	At month 24, mean logMAR VA decreased 2 letters

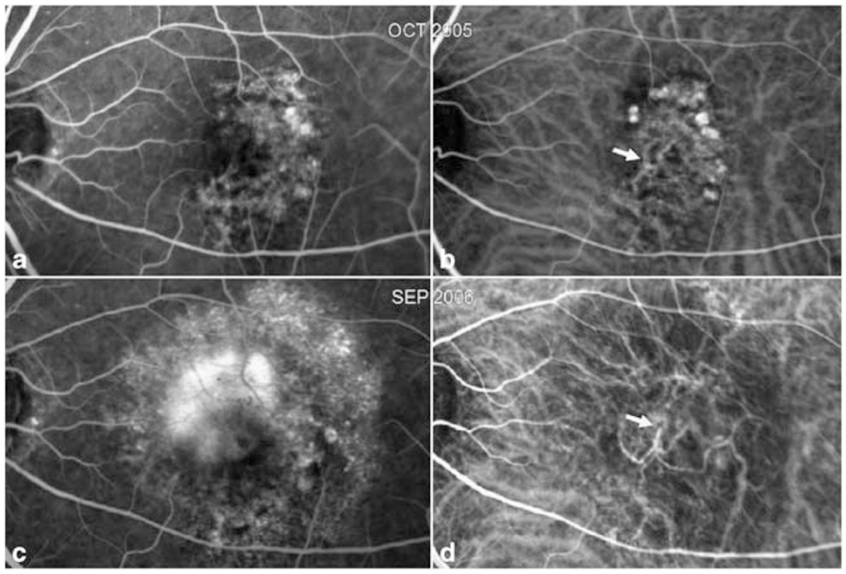

Figure 3 'Secondary CNV' following PDT for PCV: FFA before (a) and 11 months after PDT (c). CSLO-ICGA depicts the same feeder vessel in growth site (arrow), before (b) and 11 months after PDT (d) showing vascular persistence, remodeling, and expansion despite PDT.

regression.[33,34] Although most BVNs stay quiescent for long periods of time, they are by no means passive channels. Some sprout new polyps at its terminal branches (recurrence).[35] A number show continued leakage even after angiographically proven complete polyp ablation (persistence). Still others remain quiescent for months, then start to leak without any visible new polyps (reactivation).

The origin and location of these network vessels remain controversial. Some believe that they are sub-RPE in location, representing a type of CNV,[36] whereas others believe they are intra-choroidal.[37] Using a prototype of spectral domain OCT, Ojima *et al*[38] were able to identify both BVN and vascular polyp as hyper-reflectivity between RPE and Bruch's membrane, in the same tissue plane as CNV.

With the advent of confocal scanning laser ophthalmoscopy, coupled with digital dynamic ICGA (CSLO-ICGA), these network vessels are much better imaged than flash-based ICG angiography, especially the first 30 s after dye injection. Studying CSLO-ICGA, Yuzawa *et al*[39] observed that in some cases the BVN showed pulsatile flow, suggesting that they emanate from inner choroidal arterioles. The authors concluded that there may be two types of BVN, one represents intra-choroidal vascular abnormality ('PCV in the narrow sense'), the other represents neovascularization ('polypoidal CNV') that grows rapidly in the sub-RPE space.

Dynamic CSLO-ICGA also allows the identification of feeder vessels. In many cases, the vascular tree of the BVN is traceable to a single feeder vessel, possibly representing the vascular in-growth site crossing the Bruch's membrane.[40] If it is also associated with fluorescein leakage (as imaged by FFA) and overlying retinal thickening (as imaged by OCT, and observed clinically), these lesions look angiographically and behave clinically like CNV (CNV-like BVN). In a retrospective study of 52 consecutive cases of PCV, the authors found CNV-like BVN in one-third of cases (data presented at International Spectralis Meeting, Nice, 2008).

Anti-vascular endothelial growth factor therapy for PCV

Intra-vitreal anti-VEGF therapy has revolutionized the treatment for exudative AMD due to CNV. Would PCV, in particular those with CNV-like BVN, respond to anti-VEGF treatment?

Tong *et al*[41] reported increased aqueous level of VEGF in patients with PCV, though at a lower level than eyes with exudative AMD with CNV. As mentioned above, Terasaki *et al*[19] and Matsuoko *et al*[20] reported increased VEGF staining and expression on the vascular endothelium of PCV specimens. Initial clinical experience suggests that PCV respond well to anti-VEGF therapy, with rapid resolution of retinal thickening and exudate accumulation,[42,43] and increase in vision.[44]

However, both Gomi *et al*[45] and Lai *et al*[46] reported that although anti-VEGF monotherapy reduces macular thickness and improved vision in patients with PCV, the majority of the polyps remained. The data may explain anecdotal clinical cases of late recurrent massive submacular haemorrhage of patients with PCV despite initial 'successful' treatment with anti-VEGF monotherapy.

Likewise, Cho *et al*[47] reported 12 cases of presumed exudative AMD not responding to anti-VEGF monotherapy of at least 6 months' duration. PCV was diagnosed when they were later imaged with ICGA. PDT subsequently performed achieved complete resolution in 9 of 12 cases, and partial resolution in the remaining 3 cases.

Combination therapy for PCV

Understanding of the action of verteporfin PDT on polyp closure and the response of BVN leakage to anti-VEGF therapy give rise intuitively to the suggestion of combination therapy for PCV treatment. The primary rationale of proposing combination therapy for PCV is different from those proposed for exudative AMD due to CNV. In the latter condition, combination therapy aims to reduce the number of anti-VEGF re-injections through photothrombosis effect of verteporfin PDT on the CNV vasculature, and at the same time, balancing the VEGF upregulation effect of photothrombosis. For PCV, combining photothrombosis of the polyps (with the associated vascular network) with anti-vasoproliferative and anti-permeability therapy targeting the BVN aims to achieve synergistic effect by targeting different component lesions of PCV.

For this reason, the EVEREST trial was convened. It was the first randomized controlled trial investigating whether verteporfin therapy, either as monotherapy or in combination with intra-vitreal ranibizumab, is more efficacious than ranibizumab monotherapy in achieving complete polyp regression (primary outcome) as assessed by CSLO-ICGA. The secondary outcomes include visual acuity, as measured by Early Treatment of Diabetic Retinopathy Study chart, and central retinal thickness as measured by OCT. Involving seven sites in five Asian countries, the trial recruited 61 patients with symptomatic PCV with visual acuity between 24 and 73 letters on the Early Treatment of Diabetic Retinopathy Study chart. Cases were included only if the CSLO-ICGA is assessed to be typical PCV by a reading centre (Fundus Image Reading Centre, National Healthcare Group Eye Institute, Singapore). Subjects were randomly assigned to three treatment arms in 1 : 1 :1 ratio: (1) verteporfin PDT and sham injection, (2) ranibizumab intra-vitreal injections and sham PDT, and (3) combined verteporfin PDT and intra-vitreal ranibizumab injections. Results will become publicly available in 2010.

Conclusion

The understanding of PCV as a disease entity has undergone rapid evolution in the past three decades. Though differentiated by the specific features in ICGA, current understanding of the disease suggests significant overlap with exudative AMD due to CNV. Present in about one-third of Asian and one-tenth of Caucasian patients with exudative AMD, it is reasonable to be considered as a vascular subtype of exudative AMD. Seemingly better natural history, better response to PDT, and seemingly incomplete response to anti-VEGF suggest that it should be studied as a separate entity from CNV. For Caucasian patients, ICGA may be important in cases of anti-VEGF non-responders to elucidate the diagnosis of PCV. In Asian patients, ICGA may be useful for most cases of exudative AMD with occult CNV (on FFA) for proper vascular subtyping. About one-third of cases of PCV behaves angiographically and clinically as CNV, even after successful polyp ablation with focal photocoagulation of the polyps or ICGA-guided PDT of the whole lesion. Combination therapy should be considered in these cases, with evidence-based results pending from the EVEREST trial.

Conflict of interest

TH Lim had received travel support from Novartis and Heidelberg Engineering.

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