

Polypoidal choroidal vasculopathy: a comprehensive clinical update

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Abstract: Polypoidal choroidal vasculopathy as a disease is yet to be comprehended completely. The clinical features consisting of huge serosanguineous retinal pigment epithelial and neurosensory layer detachments, although unique may closely mimic neovascular age-related macular degeneration and other counterparts. The investigative modalities starting from indocyanine angiography to optical coherence tomography angiography provide diagnostic challenges. The management strategies based on the available therapies are plenty and not vivid. A detailed review with clarifying images has been compiled with an aim to help the readers in getting a better understanding of the disease.

Keywords: aflibercept, indocyanine green angiography, optical coherence tomography angiography, photodynamic therapy, polypoidal choroidal vasculopathy, polyps, submacular haemorrhage

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Introduction

Polypoidal choroidal vasculopathy (PCV) is characterised by multiple recurrent serosanguineous bilateral retinal pigment epithelial detachments (PEDs). It was first described by Stern and colleagues¹ in the 1980s and was initially presumed to be a choroidal vasculature abnormality predominantly arising in the peripapillary area.^{2–4} PCV resembles neovascular age-related macular degeneration (AMD) in its morphological features.³ However, the clinical course of PCV is more stable and visual outcomes are more favourable from those of AMD.^{2,5–13} With the advent of multimodal imaging modalities, new insights have been obtained in the pathogenesis, clinical features and management of PCV.

History

The term ‘idiopathic polypoidal choroidal vasculopathy’ was first coined by Yannuzzi and colleagues. In 1982, Yannuzzi and colleagues² recognised a variant of the choroidal neovascular membrane (CNV) in the peripapillary area, which was polypoidal in appearance and associated with

multiple serosanguineous PEDs. Later in 1984, Kleiner and colleagues³ reported a series of such patients at the American Academy of Ophthalmology meeting and termed this distinct abnormality as ‘Posterior uveal bleeding syndrome’. Later, Stern and colleagues¹ elaborated on similar clinical findings in a group of middle-aged African women.

Yannuzzi and colleagues⁵ identified characteristic dilated and branching inner choroidal vessels and reddish-orange polyp-like aneurysmal dilatation of these vessels in these patients. They believed that these polypoidal vascular lesions were responsible for recurrent serous and haemorrhagic PEDs. Only larger polyps could be recognised clinically, else fundus fluorescein angiography (FFA)/indocyanine green angiography (ICGA) was necessary for the definitive diagnosis.⁵ Yannuzzi and colleagues⁵ introduced the term ‘polypoidal choroidal vasculopathy’ based on the clinical findings in a larger group of patients. They reported that this entity was noticed in white patients too, although it was more common among pigmentary races.^{2,6}

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Initially, PCV was considered as a distinct entity, but later in the 1990s, the reported spectrum of PCV cases expanded to include cases with features of neovascular age-related macular degeneration (nAMD). Coscas and colleagues,¹⁴ in an article, suggested classifying PCV into two variants: the idiopathic variety and the nAMD type. According to the authors, the idiopathic type seemed to be more commonly associated with haemorrhagic detachments, the presence of a branching vascular network (BVN), increased choroidal thickness and better visual outcomes due to lesser intraretinal changes.¹⁴ On the contrary, the nAMD type was associated with chorioretinal atrophy, drusen, the absence of BVN, the presence of a type 1 CNV and poorer visual outcomes.¹⁴

Pathogenesis

PCV is considered to be a primary abnormality of inner choroidal vessels. The affected vessels tend to bulge causing polypoidal protrusions, due to the defective lining secondary to minimal pericytes and thinned out endothelial cells.^{15,16}

The cause of such manifestations remains a controversy. A study by Okubo and colleagues¹⁷ based on biomicroscopy supports a mechanism similar to branch retinal vein occlusion (BRVO). A dilated tortuous venule was noted adjacent to a sclerosed arteriole by the author.¹⁷ The compression of the venule induced at the arterio-venous crossing site may cause stasis leading to fragility, tissue degeneration, polypoidal configuration, leakage and tendency to rupture and bleed. ICGA findings showing a slow filling of the polyps in the early phase and leakage in the later phase also support this theory.

Nakashizuka and colleagues¹⁸ identified certain features which differentiate PCV from CNV based on histopathology and immunobiochemistry. In PCV, the choroidal vessels showed more hyalinisation, massive exudation, lesser granulation tissue and absence of CD34 (a marker of vascular endothelial expression seen in hypoxia).¹⁸ Using high-speed confocal Scanning Laser Ophthalmoscopy (SLO)-assisted ICG, Yuzawa and colleagues¹⁹ conducted a study to elucidate the pathogenesis and origin of these abnormal vessels. These vessels seemed to originate from the inner choroid. Based on their findings, they classified PCV into three subtypes.¹⁹ The first one had a primary choroidal vascular abnormality; the second one was the rapidly expanding polypoidal CNV and the third type one was seen post

radiation therapy. The first variant originated from the inner choroidal vessels comprising larger calibre branching vessels showing pulsation with lack of late phase staining. The second variant had features of CNV reaching the subretinal or subretinal pigment epithelial space with thinner leaky vessels but additionally having polypoidal protrusions.

As the PCV lesions evolve, they increase in size and may also become leakier. How these changes occur is not certain. Various proposed mechanisms include simple vessel hypertrophy with progression towards the edge of a vascular channel or unfolding of the aneurysmal elements leading to tubule formation. On ICGA, these changes are evident as a mass-like lesion protruding towards the outer retina initially and later flattening out and expanding tangentially indicating unfolding of the aneurysmal component.²⁰

A recent study by Kumar and colleagues²¹ emphasised the role of protease high-temperature requirement factor A1 (HTRA1) overexpression, in the initiation of polyp formation by altering extracellular matrix remodelling. With experimental mouse models, they suggested that the subsequent evolution of the disease is inflammatory, characterised by features like immune complex deposition, activation of complementary cells and inflammatory cell infiltration.²¹

Subhi and colleagues have explored the role of monocytes in the pathogenesis of PCV. Overexpression of CD11b and CD 200 in the circulating monocytes, in an angiographic subset of PCV with prominent BVN, signifies their role in triggering the disease process.²² CD11b and CD200 are also highly expressed in CNV cases, implying similar pathogenic mechanisms of CNV and the BVN associated with PCV.²² Furthermore, Subhi and colleagues²³ did a prospective study on the expression of chemokine receptors CCR2 and CX3CR1 in circulating monocytes in patients of PCV and found that the angiographic variety with prominent BVN had increased expression of these receptors than the type without BVN. The authors suggested that the CCR2-positive monocytes play an essential role in CNV formation, but the expression of CX3CR1 regulates the angiogenic drive and vascular network development.²³

PCV differs in terms of T-cell immunity as compared to AMD.²⁴ Whereas AMD patients have accelerated CD8T-cell differentiation and ageing,

PCV patients have a similar expression of CD8T-cell differentiation and ageing markers as compared to healthy controls.²⁴ All these studies show that PCV is not only an immunological entity distinct from AMD but is very heterogeneous in itself.

Genetics

Genes associated with PCV are also integral to the complement cascade, inflammatory pathway, extracellular matrix/basement membrane regulation pathway and lipid metabolism.²⁵ There is an overlap of many genes between PCV and AMD.²⁵ Single-nucleotide polymorphism (SNP) in a few genetic loci like age-related maculopathy susceptibility 2 (ARMS2), HTRA1, complement factor H (CFH), complement component 2 (C2), complement factor B (CFB), RD RNA-binding protein (RDBP), Super killer viralicidic activity 2-like (SKIV2L), cholesterol ester transfer protein (CETP), 8p21 and 4q12 have been found to be significantly associated with PCV.²⁵

The only SNP found significantly different between PCV and AMD is rs10490924 in ARMS2/ LOC387715 gene with lower frequency in PCV.²⁵ ARMS2 encodes a mitochondrial protein in the neurosensory retina. This genotype has been found to be associated with worse phenotype and poor response to treatment.²⁵ The HTRA1 gene overexpression induces development of choroidal BVN and polypoidal lesions via incompletely understood mechanisms. The significant association between CFH/C2 polymorphisms and PCV suggests that the complement system is dysfunctional in PCV as in AMD.²⁵

Recently, Huang and colleagues have reported the role of a missense variant of FGD6 gene (Lys329Arg) in increasing the susceptibility of the disease (odds ratio = 2.12). FGD6Arg variant up-regulates the development of abnormal vessels greater than the Lys variant.²⁶

Risk factors

Systemic risk factors

Cardiovascular abnormalities have been associated with PCV.^{27–30} About 41%–45% of PCV patients have associated systemic hypertension.^{27–29} Raised plasma viscosity and thrombocytopenia have been associated with PCV.³¹

Patients with obstructive sleep apnoea (OSA) have increased levels of circulating epinephrine and norepinephrine.³² With elevated levels of catecholamine, OSA has been hypothesised to be a direct risk factor for central serous chorioretinopathy (CSC) which in turn is related to PCV.³²

Diabetes mellitus (DM) is more likely to be associated with CNV-AMD than in PCV.²⁷ Since vascular endothelial growth factor (VEGF) levels are raised in uncontrolled DM,^{33,34} the preponderance of nAMD in DM than in PCV indirectly indicates the fact that high VEGF levels are not responsible for initiating PCV. Aqueous concentration of VEGF is also found to be low in PCV than in nAMD.³⁵ Habitual cigarette smoking is found to be a risk factor for PCV.²⁹

Ocular risk factors

Choroidal thickening has been found to be associated with PCV. The PCV spectrum of patients has increased choroidal thickness when compared to those with nAMD.³⁶ Similarly, CSC, which is by itself characterised by choroidal thickening, is also a potential risk factor for the development of PCV.^{37–40} Both the diseases hence may share similar lines of pathogenic mechanisms, but the ultimate evolution into different phenotypes warrants further studies.

Serum biomarkers

C-reactive protein. C-reactive protein (CRP) is a marker of acute systemic inflammation. Immune-mediated inflammation is characteristic of AMD, and therefore, high CRP levels are often found in AMD patients.⁴¹ However, the studies contradict each other regarding the role of CRP in pathogenesis of PCV.^{42–44} While Cheng and colleagues⁴² found no significant relationship between the two and suggested PCV to be a chronic inflammatory disease rather than an acute disease, Kikuchi and colleagues⁴³ reported high CRP levels to be associated with significantly increased risk of PCV. Subhi and colleagues⁴⁴ also found that CRP levels are increased in PCV patients as compared to controls, but other markers of inflammation such as interleukin (IL)-1 β , IL-6 and IL-10, which are otherwise increased in AMD, were found to be similar to controls. Perhaps, PCV has a complex inflammatory profile that needs further characterisation.

Homocysteine. Cheng and colleagues⁴² from their prospective case-control study reported that each 1 µmol/L increase of serum homocysteine levels caused a corresponding 1.5-fold increased odds of developing PCV. High serum levels of homocysteine, which is known to cause endothelial injury secondary to increased oxidative stress,⁴⁵ may be responsible for inducing similar damage to the choroidal arteries leading to arteriosclerosis and polypoidal aneurysmal dilations.¹⁸

Matrix metalloproteinases. Increased serum levels of matrix metalloproteinase (MMP) have been demonstrated in PCV. Zeng and colleagues⁴⁶ found a rise of MMP 2 and MMP 9 in PCV patients. MMPs play an important role in extracellular matrix remodelling, which is believed to influence the pathogenesis of PCV.^{18,47}

Demographics

Among the presumed nAMD cases, the prevalence of PCV is 7.8% in American,⁶ 4.0% in Belgian,¹² 5.7% in Danish,⁴⁸ 9.8% in Italian,⁴⁹ 9.1% in Caucasian,⁵⁰ 8.2% in Greek,⁵¹ 23.0%–54.7% in Japanese,⁵² 22.3%–49% in Chinese⁵³ and 24.6% in Korean populations.⁵⁴ The prevalence differs with the age.⁵⁵ The prevalence of PCV is higher in blacks, Japanese, Chinese and other Asians than in whites, while AMD incidence is high in whites as compared to blacks.⁵⁶ In the Asian population, both PCV and AMD are more prevalent.

In a study done in an Indian population by Anantharaman and colleagues,⁵⁷ it was found that PCV was more prevalent in males and was more commonly unilateral (95.5%) with a mean age at presentation being 61.06 years. A few studies have shown higher rates of bilateral PCV occurrence, estimated to be around 24% in Koreans cohort⁵⁴ and 10% in Japanese cohort.⁵²

Age

The average age group affected falls in the range of 50–65 years, with the mean age being 60.1 years.²⁰ Considering population-wise data, the average affected age among the Korean,⁵⁴ Chinese,⁵³ Japanese⁵² and the Indian population⁵⁷ is found to be 64.6, 65.4, 72.8 and 60.06 years, respectively. The mean age of presentation of PCV in Caucasians is 75.4 years.⁵⁰ PCV patients present early than AMD cases, more so in whites (≈4 years) as compared to the Asian race (≈1 year).⁵⁶

Sex

Initially, it was believed that PCV exclusively occurs in women, but later it was noted that women are predominantly affected at a ratio of 4.7:1.²⁰ Recent studies indeed show that men are more commonly affected than women in the Asian population, unlike the Caucasians.⁵⁸ The distribution is not different while comparing PCV with AMD.⁵⁶

Race

PCV has almost fourfolds increased predilection towards pigmented races.⁵⁹ Those belonging to the African and Asian descent are more commonly affected.^{1,59}

Clinical features

The dilated choroidal vascular channels terminating as polyps are clinically seen as an orange bulging lesion in the macular and peripapillary area. These lesions are not easily evident unless the comprising vascular component is large enough and the overlying retina is flat. These are commonly associated with serous and serosanguineous PEDs (Figure 1). Sometimes micro rips may occur at the margin of the PED.⁶⁰ The intraretinal and subretinal lipid deposits indicate the chronicity of disease.^{55,57} Drusen are detected in 23%–55% cases.⁶¹ In the long term, the fibrous scarring is minimal, and it is determined by the associated haemorrhagic component.⁶²

The vascular lesions are mostly found in the peripapillary area, although recent literature suggests that they could also be present at the macula¹⁰ and in the mid-periphery.⁹ Asian ethnic groups may have a higher incidence of the macular polyps (up to 74.5%).⁵⁷

The presenting visual acuity is surprisingly better irrespective of the PEDs due to minimal damage to the intraretinal structures. Multiple polypoidal lesions may be present in the same eye. There is a marked tendency towards bilateral involvement. The fellow eye is at high risk of developing similar clinical changes, which can be picked up with ICGA.⁶²

Sometimes, PCV may masquerade as Central serous chorioretinopathy (CSCR). Multiple serous PEDs and NSDs with retinal pigment epithelium (RPE) atrophy may warrant an ICGA. A careful search of polyps is ideal in such

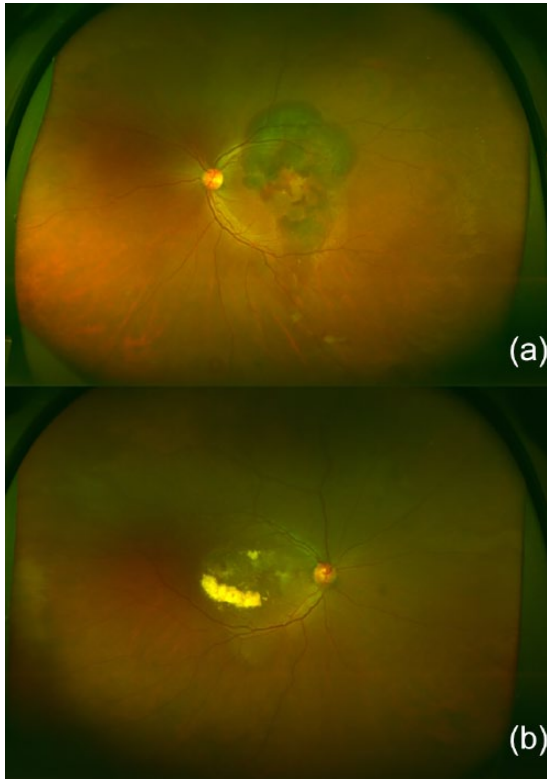


Figure 1. Optos ultra-widefield fundus photographs of a patient who had a bilateral asymmetrical presentation of polypoidal choroidal vasculopathy. (a) Fresh massive submacular haemorrhage is evident in the left eye. (b) Fundus of the right eye shows old submacular hard exudates with resolving subretinal fluid.

cases as the visual prognosis and management strategies are different.⁷ A clinical presentation of CNV may at times reveal polyps on ICGA. Various studies show that 4%–9.8% of patients with CNV are later diagnosed as PCV on ICGA.^{12,63} Peripheral location of the polyps may cause peripheral exudative haemorrhagic chorioretinopathy. Such lesions are most commonly detected in the temporal periphery. Most of the peripheral polyps follow a benign course with spontaneous resolution while a few may lead to significant subretinal haemorrhage threatening the macula requiring aggressive therapy.⁶⁴ Sometimes, the subretinal and sub-RPE bleed may mimic a mass lesion. Some of these cases have been initially misdiagnosed as choroidal melanoma.⁶⁵

Natural course

The natural history of the disease varies depending on the genetic and the racial background. As

mentioned in the genetics section, the ARMS2 SNP genotype has worse phenotypic features such as larger lesions and increased risk of vitreous haemorrhage and poor response to therapy.²⁵ The Caucasians have relatively more peripheral lesions as compared to the Asians who have macular preponderance.⁶⁶ This may be the reason for poor baseline visual acuity in Asians but better treatment outcome in the form of visual gain.⁶⁶ The anatomical features like the location (peripapillary *versus* macular), size of the lesion, associated amount of bleeding and exudation, rapidity of its resolution and the extent of fibrosis ultimately determine the visual acuity.⁶⁷

PCV is mostly a chronic disease with a variable course. In one of the studies, it was seen that almost 50% showed a favourable course with the resolution of polyps over a period of 3 years whereas the other half showed recurrent bleeding and fibrosis resulting in photoreceptor degeneration and vision loss. Eyes, which had polyps with a cluster of grapes appearance (as detected on ICGA), showed a haemorrhagic course associated with poorer outcomes.⁵⁹ A recent study pointed out that certain baseline features like the absence of submacular haemorrhage, larger lesion size and presence of a cluster of polyps on ICGA are associated with reactivation.⁶⁸ Long-term visual outcomes with or without treatment are poor as more than half of the baseline cases show deterioration in vision in spite of treatment due to haemorrhage and scarring.⁶⁹

Clinical imaging

Figures 2–7 are shown in the following.

Optical coherence tomography

Optical coherence tomography (OCT) provides high-resolution cross-sectional images of the retina. It is a non-invasive modality helpful in detecting morphologic changes in the retina and choroid. Findings in OCT are well correlated with the histopathological changes seen in PCV.¹⁷ With the evolution in techniques, the modern day spectral domain and swept source OCT provide an improved demarcation of the outer retinal layers *in vivo* and help in better localisation of the PCV lesions.⁷⁰

Various OCT signs of PCV have been described. Characteristic dome-shaped elevations of the highly reflective RPE with

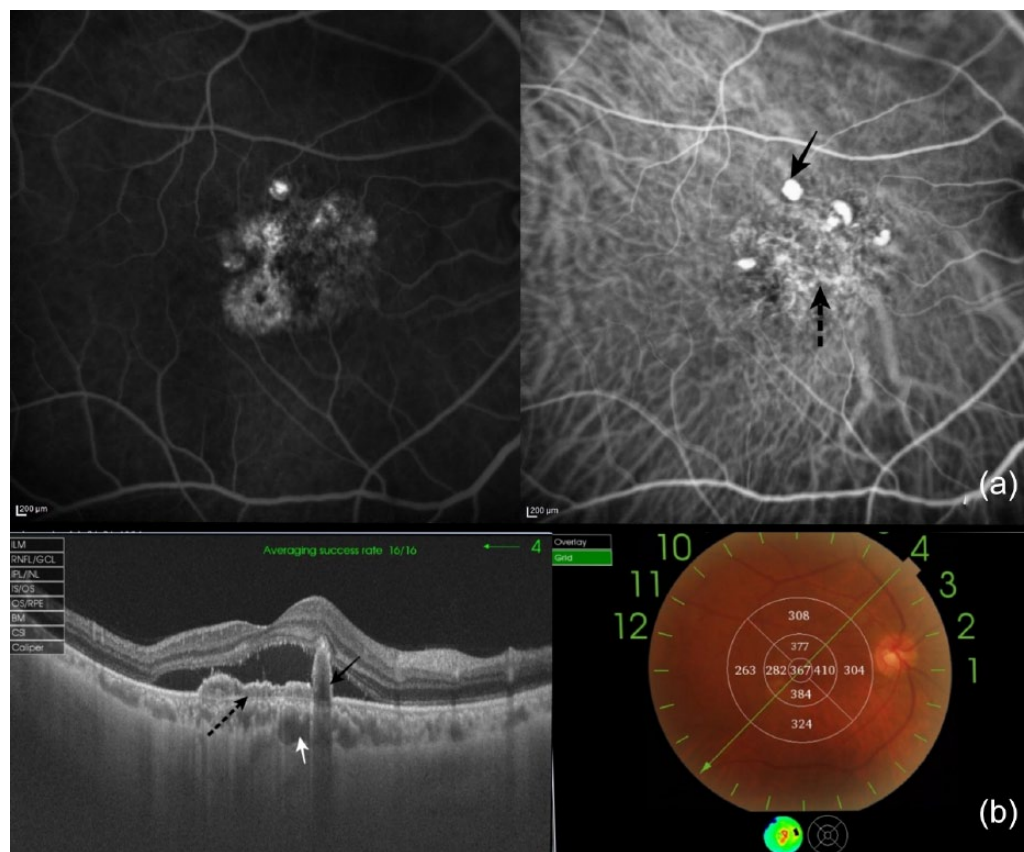


Figure 2. (a) Fundus fluorescein angiography/indocyanine green angiography showing multiple focal hyperfluorescence/hypercyanescence with a faintly seen dark halo suggestive of polyps (black arrow). The branching vascular network (dotted arrow) can be seen in between the polyps. (b) Swept source optical coherence tomography showing thumb shaped pigment epithelial detachment (black arrow), double layer sign (black dotted arrow) and dilated choroidal vessel in the Haller's layer (white arrow).

moderate internal reflectivity within the PED, suggestive of the polypoidal activity have been described by Iijima and colleagues.⁷¹ A tomographic notch may be seen between two PEDs representing a thumb-like polyp.⁷⁰ Peaking of PEDs is another distinctive feature denoting the location of lesion beneath Bruch's membrane. According to Iijima and colleagues, a lesion containing fluid can exhibit a steep configuration only if the surrounding wall is thick and tough. Hence, a serous PED shows a smooth dome-shaped wall whereas a PED with an underlying polyp lifting the tougher Bruch's membrane shows peaking.⁷²

The double layer sign consists of two highly reflective layers, the inner layer being the RPE and the outer reflective layer corresponding to the inner boundary of the Bruch membrane/choriocapillaris complex. It is thought to represent the area of the BVN with or without the surrounding

fluid extravasation. If associated with a neurosensory detachment, it indicates disease activity.⁷³

Along with ICGA, OCT is helpful in making the diagnosis of ICGA. OCT being non-invasive can be used as a screening tool. In a study by De Salvo and colleagues,⁷⁴ a sensitivity of 94% and specificity of 92% was seen when multiple PEDs, sharp PED peaks, PED notches and polyp lumens adherent to the underside of the PED were used as diagnostic criteria for PCV based on Spectral domain optical coherence tomography (SD-OCT) (when at least 3 out of 4 were positive). In a study by Liu and colleagues,⁷⁵ pigment epithelium detachment, double layer sign, and thumb-like polyps were found to be more common in PCV eyes than in nAMD eyes. When two out of these three signs were used for the diagnosis of PCV, a sensitivity of 87.5% and specificity of 86% was found.⁷⁵ OCT is further an indispensable tool in monitoring patients with PCV following therapy.⁷⁶

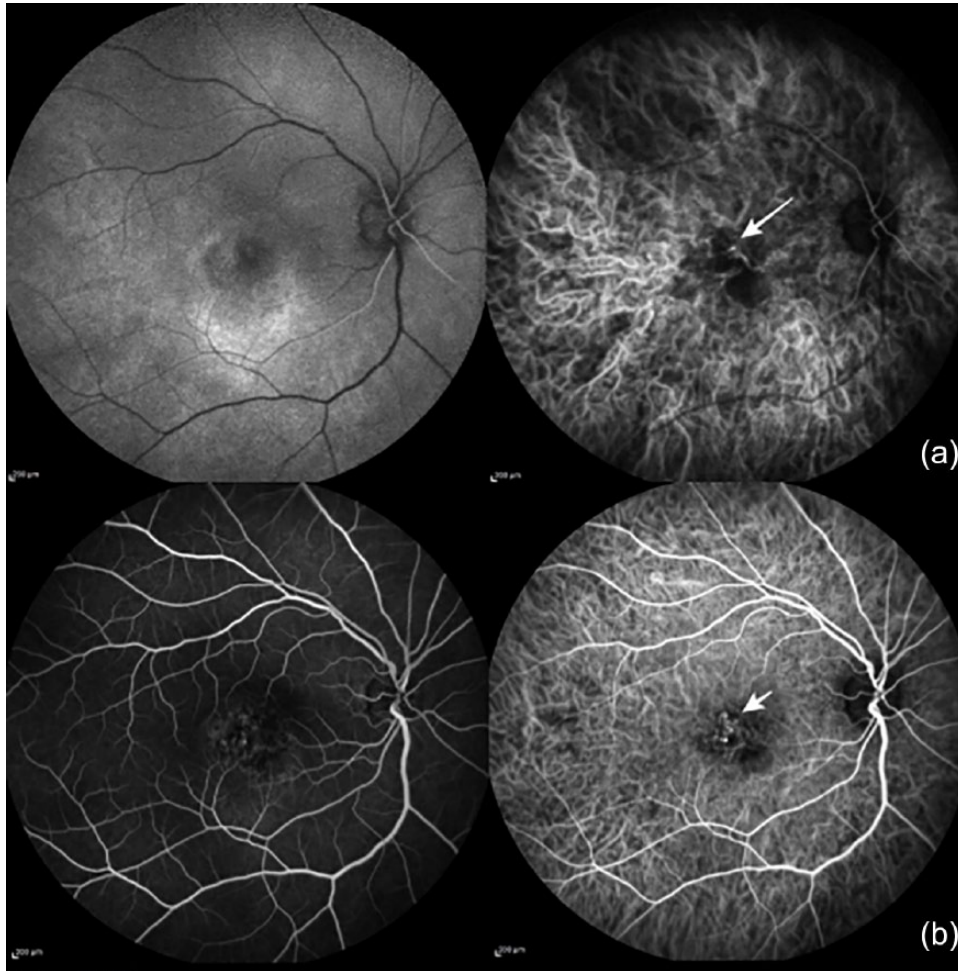


Figure 3. (a) Early phase fundus fluorescein angiography with corresponding indocyanine green angiography showing localised hyperfluorescence (white arrow) in the macular region (b) The polyps enmeshed in the branched vascular network can be clearly seen in the late phase.

Prominent choroidal changes have been noted in cases of PCV. The enhanced depth imaging optical coherence tomography (EDI-OCT) and swept source OCT help in better imaging of the choroidal structures.⁷⁷ Increased subfoveal choroidal thickness with dilated choroidal vessels is a notable feature. The diameter of these dilated vessels ranges from 146 to 358 μm . Increase in choroidal thickness is usually associated with choroidal hyperfluorescence.⁷⁸

Fluorescein angiography

FFA features of PCV are similar to that of occult CNV.^{79,80} A diffuse stippled hyperfluorescence is noted in the area of the lesion with no evidence of a classic component. Rarely, the polyps are also visible. The shorter wavelength in FFA as compared to ICGA cannot pass effectively through

the RPE and thus fails to highlight the choroidal abnormalities. Also, fluorescein has a lower affinity to plasma protein as compared to ICG and leaks profusely through the choriocapillaris. This may mask the underlying polypoidal lesions and branch vascular network. But on the contrast, FFA may be beneficial in marking the lesion area for assessing the greatest linear dimension (GLD) as ICG fails to cover PEDs and NSDs due to poor permeability. Gomi and colleagues⁸¹ in their study have proposed that a combination of FFA with SLO-based ICGA helps in identifying the maximal size of the PCV lesion.

Tan and colleagues have classified PCV based on FFA and ICGA features helping to prognosticate the baseline cases. The three categories proposed by them include PCV with interconnecting channels, with leaking BVN and with non-leaking

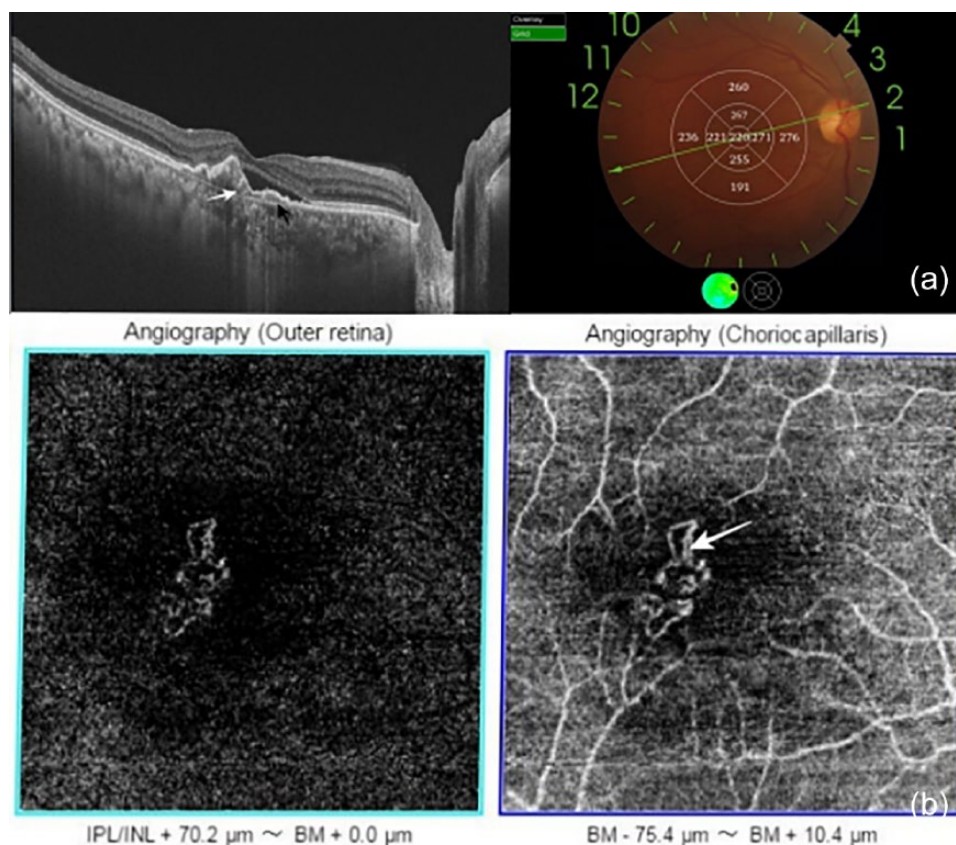


Figure 4. (a) Swept source optical coherence tomography (OCT) line scan of the same patient mentioned in Figure 3 – showing double layer sign corresponding to the branched vascular network (BVN) and elevated notched pigment epithelial detachment indicating the presence of polyps. (b) The well-delineated BVN (white arrow) with faintly visible polyps can be seen on swept source OCT angiography at the outer retinal-choriocapillaris level.

BVN. The third variant showed the poorest long-term visual outcomes.⁸²

Indocyanine green angiography

ICG dye is 98% protein bound, has poor permeability and fluoresces in the near-infrared range (790–805 nm). The retention of ICG in the chorioidal circulation makes it ideal for imaging chorioidal circulation. As the operating wavelength is longer, it can fluoresce better through pigment, fluid, lipid and haemorrhage than fluorescein dye. Presently, ICGA is the investigation of choice to confirm the diagnosis of PCV.

ICGA is indicated when serosanguineous maculopathy is associated with one or more of the following features: massive submacular haemorrhage, presence of subretinal orange nodule, lack of a marked response to anti-VEGF, notched PED, double layer sign on swept source optical

coherence tomography (SSOCT), as these cases may have a pachychoroid pathology like PCV.⁷⁶ FFA alone may not pick up the changes in the inner choroidal vasculature and based on FFA alone, these could be misdiagnosed as cases of occult or minimally classic CNV.⁵

A typical polyp appears as an early hyperfluorescent nodule with a halo of hypofluorescence around the nodule. The presence of orange-red subretinal nodules with corresponding ICG hyperfluorescence is considered pathognomonic of PCV.⁸³ Majority of the polyps appear within the first minute of ICGA,⁸⁴ although the EVEREST study recommended a time window of 5 min in which the polyps of PCV appear after injection of ICG dye.⁸⁵

The late phase of angiogram may be associated with a reversal of the pattern of fluorescence observed in the initial phases. The area

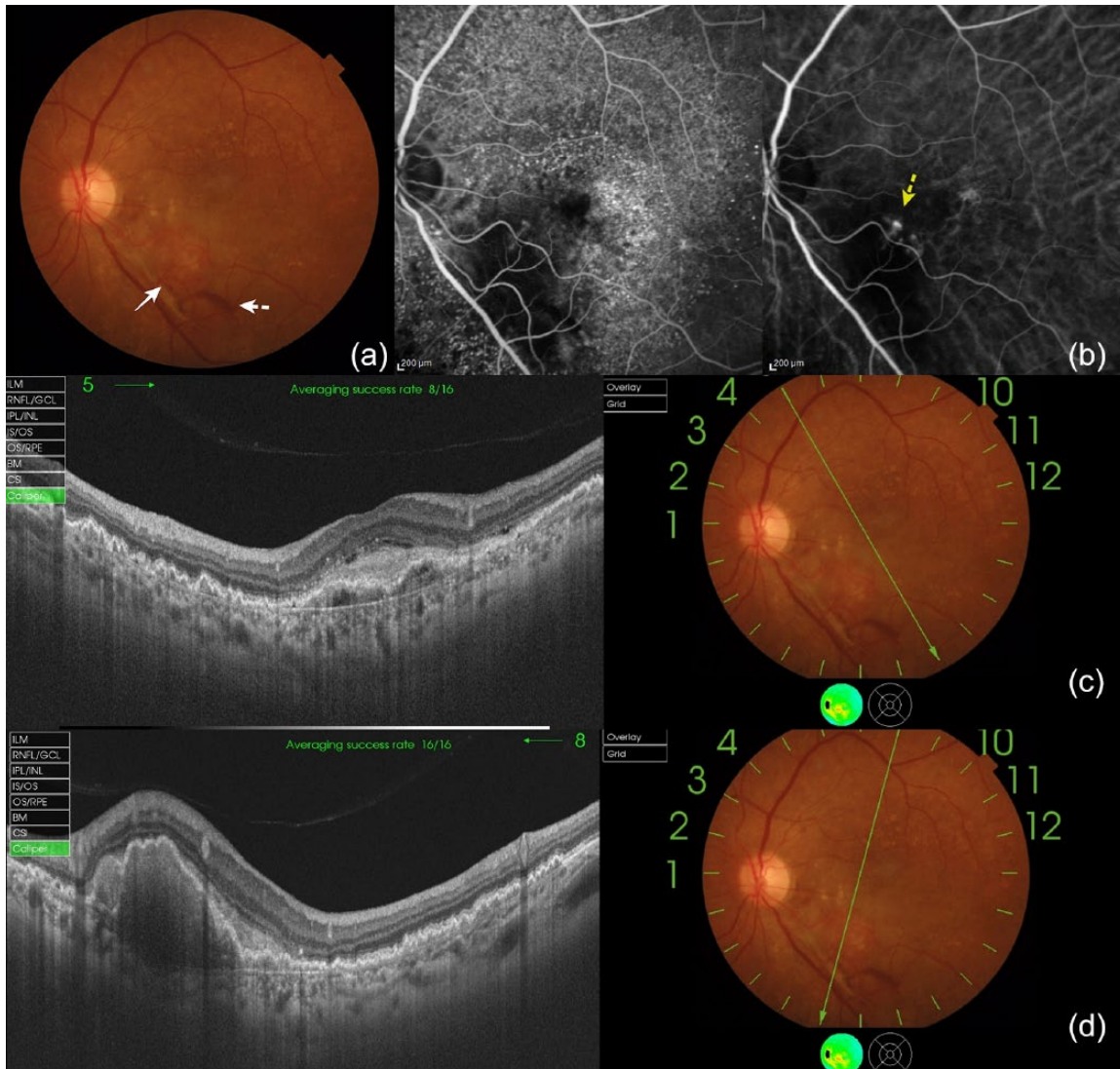


Figure 5. Multimodal imaging of an atypical presentation of polypoidal choroidal vasculopathy. (a) Fundus photograph showing reddish subretinal nodular lesion inferior to the macula (white arrow) with a streak of subretinal bleed (white dotted arrow). The foveal reflex is dull with a probable presence of fibrous scarring and surrounding drusen. (b) Fundus fluorescein angiography showing multiple dotted hyperfluorescence caused by cuticular drusen with blocked fluorescence corresponding to the subretinal nodule. The polyps (yellow dotted arrow) are evident on the indocyanine green angiography image with a connecting branching vascular network extending till the fovea. (c) Swept source optical coherence tomography (OCT) image – line scan through the fovea showing fibrovascular pigment epithelial detachment (PED) with subretinal hyperreflective scarring. (d) Swept source OCT – line scan through the subretinal nodule showing a raised notched PED due to the polypoidal lesion.

surrounding the lesion becomes hyperfluorescent, and the centre of the lesion demonstrates hypofluorescence.⁸⁵ This helps in determining the activity of polyps. The polyps may be solitary or multiple. Different morphological patterns have been described: a ring (or ‘whorl’ pattern) or cluster (or ‘bunch of grapes’), the latter carrying a worse prognosis. Although the majority of

polyps are macular, polyps can also be classified based on location as^{11,86}

- peripapillary (within one disc diameter of the optic disc),
- subfoveal,
- juxtafoveal (within 200 μm of fovea),
- extrafoveal.

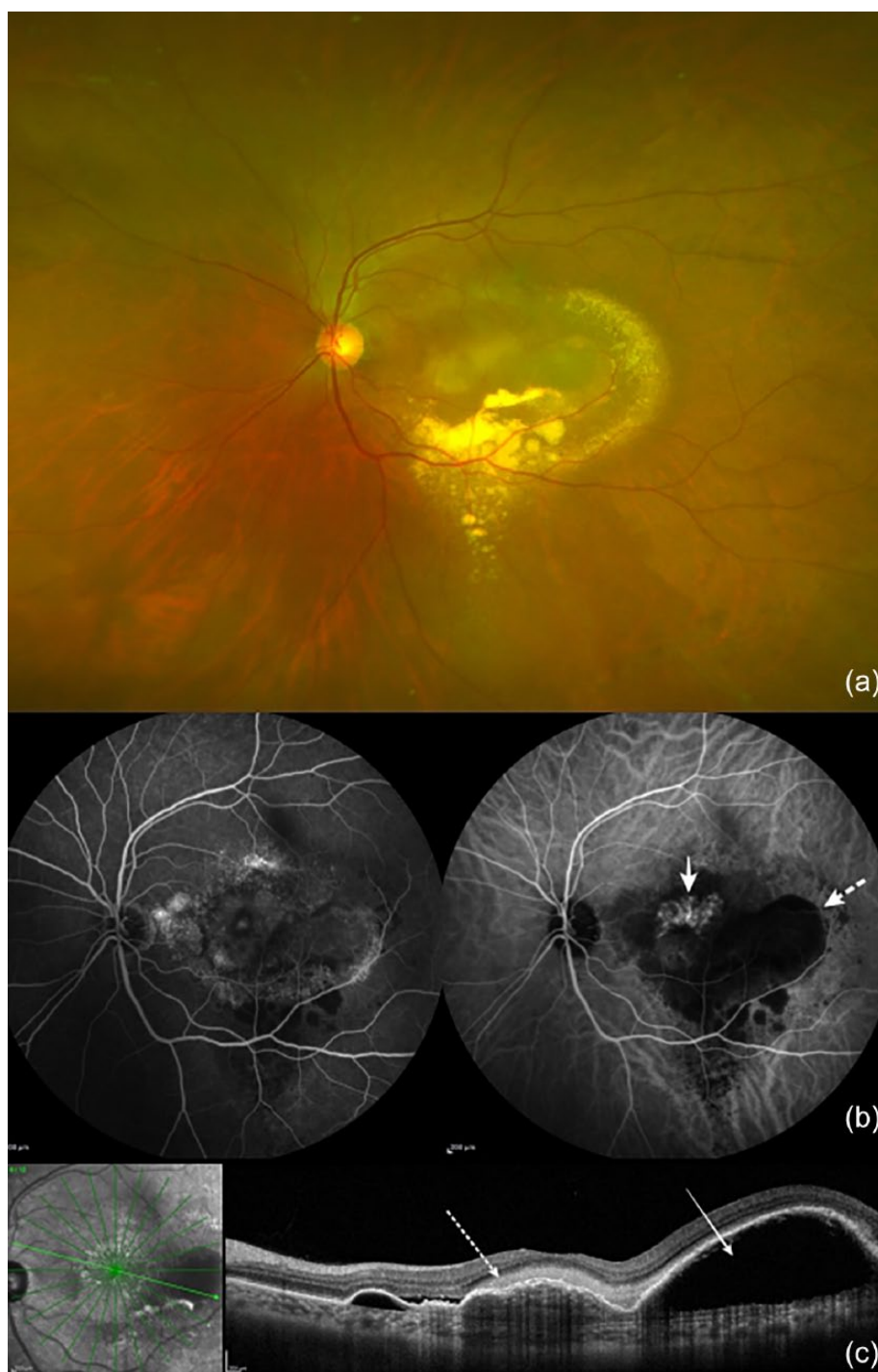


Figure 6. (a) Optos fundus imaging of a patient with treatment-resistant polypoidal choroidal vasculopathy (PCV). (b) Indocyanine green angiography showing residual PCV complex with relatively mature vessels (white arrow) and blocked fluorescence (dotted arrow). (c) Optical coherence tomography through the PCV complex illustrates presence of scarring (dotted arrow) and long-standing serosanguineous pigment epithelial detachment (white arrow) responsible for the blocked fluorescence.

On dynamic ICGA, abnormal vessels corresponding to the BVN can be seen in about 70% cases.⁸⁷ Based on this, Spaide and colleagues⁸⁸

classified PCV into 2 types: Type 1 (polypoidal CNV): polyps with characteristic BVN (both feeder and draining vessels); Type 2 (typical

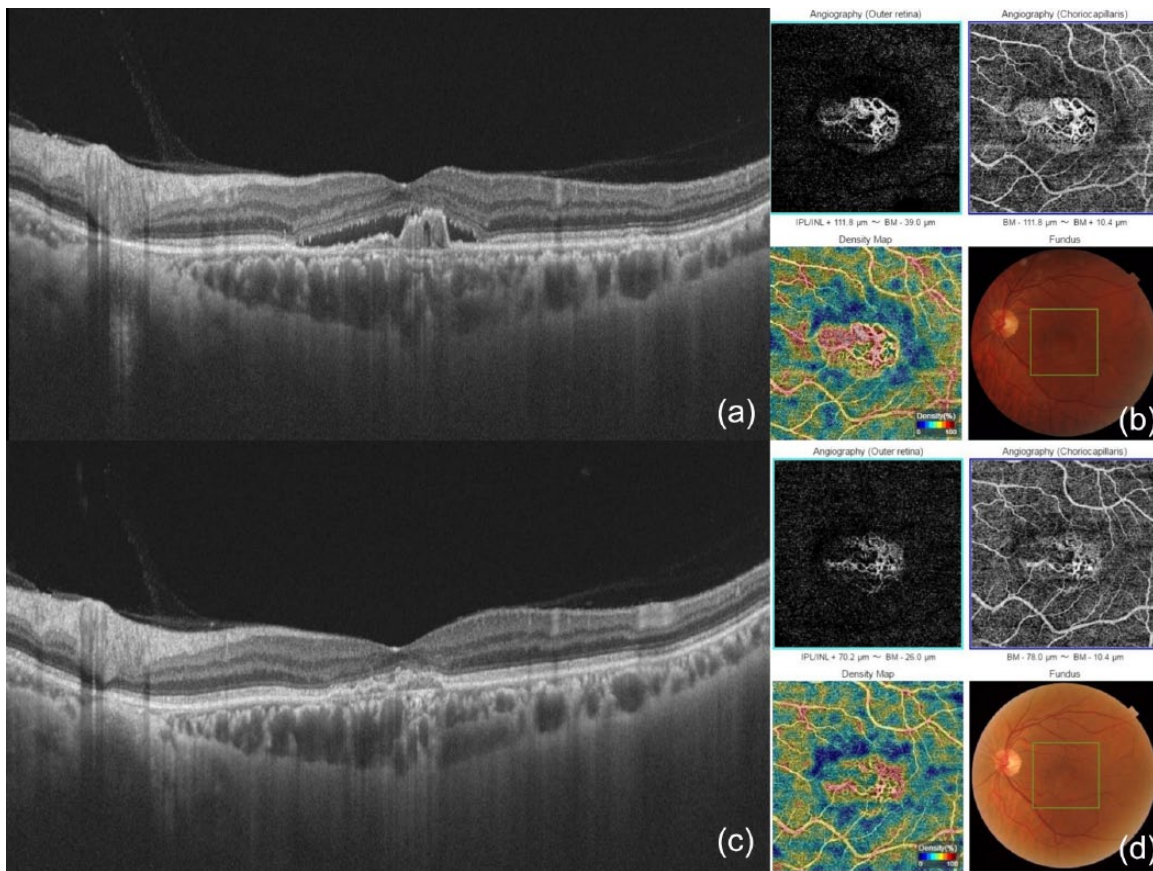


Figure 7. Optical coherence tomography (OCT) angiography is a useful tool in monitoring progression. (a) Baseline swept source OCT image shows a double layer sign with a thumb-like pigment epithelial detachment (PED) associated with overlying subretinal fluid (SRF) and dilated choroidal vessels. (b) The branching vascular network simulating Medusa head along with high-flow polyps is evident on the OCT angiography. (c) Post loading – three monthly injections of aflibercept, the patient had a drastic reduction in SRF and PED along with (d) reduction in both intensity and size of lesion on OCT angiography.

PCV): polyp with absent BVN (neither feeder nor draining vessels). Also, pulsatile fill of polyps on dynamic ICGA is a characteristic feature of PCV.

The Everest study has further described the imaging standards and grading protocol of PCV.⁸⁵ PCV is diagnosed based on early subretinal ICGA hyperfluorescence (appearing within the first 5 min of ICG dye injection) and at least one of the following diagnostic criteria:

- Nodular appearance of the polyp on stereoscopic viewing;
- Hypofluorescent halo around the nodule;
- Abnormal vascular channel(s) supplying the polyps;
- Pulsatile filling of polyps;

- Orange subretinal nodules corresponding to the hyperfluorescent area on ICGA;
- Massive submacular haemorrhage.

Submacular haemorrhage occurs as a frequent complication off PCV. As stated previously, ICG can fluoresce through haemorrhage and thus becomes indispensable in the diagnosis of PCV especially when other modalities of diagnosis cannot be used in the presence of haemorrhage. Hence, ICGA is the gold standard for diagnosis of PCV.

Polyps in cases of PCV are generally picked up well on ICGA. BVN and pulsatile hyperfluorescence have not been reported in all cases on ICGA and require dynamic imaging. It has been seen that optical coherence tomography angiography

(OCTA) is a better modality for characterisation of BVN.⁸⁹ ICGA has to be performed with caution in patients with liver disorders as ICG is primarily metabolised in the liver.

Optical coherence tomography angiography

OCTA is a novel non-invasive imaging modality that helps in *in vivo* visualisation of retinal and choroidal vasculature. This modality helps in distinguishing flow within the vessels from motionless tissues by utilising several protocols like split-spectrum amplitude-decorrelation (SSADA), phase variance and speckle variance and so on.⁹⁰ OCTA guides in the better axial localisation of the pathology, unlike FFA and ICG.⁹¹

OCTA helps in better visualisation of BVN. The BVN is constantly visualised as hyperflow structure (55%–100% detection rate) due to the linear blood flow within these vessels.^{87,89} These high flow vessels are recognised at the level of Bruch's membrane as supported by the histopathological studies. The BVN complex flow is detected at an average of 28.6µm below the RPE reference plane as proposed by a recent OCTA guided study by Chi and colleagues.⁹² Different patterns like sea-fan, tangled and Medusa head have been described based on the morphological appearance of the BVN.⁸⁹

The polyp detection rate is low (50%–75%), although higher detection rates up to 93% have been reported.^{89,93,94} The polyp is mostly identified as a hypoflow round structure or as a hyperflow lesion with a surrounding hypointense halo. It is suspected that the low flow status does not indicate the absence of circulation rather points to the fact that the level of flow is not within the detectable range of OCTA. It is hypothesised that the circulation within the polyp can be too turbulent to be sensed. The non-uniform flow is further explained by histopathological reports that have demonstrated partial obstruction of polypoidal lumen because of the combination of vessel hyalinisation, thrombus formation, basement membrane thickening and neutrophil adhesion to the vessel wall. The flow in the polypoidal lesion is noticed at an average of 45.3µm above the RPE reference plane. The active flow is mostly localised in the saccular structures lying beneath the roof of a PED. Various polyp morphological flow patterns like cluster, nodules, ring and dot have been described.^{87,92,93}

OCTA guides in understanding the anatomy and pathophysiology of PCV. Recently, Chi and colleagues have reported the existence of a choroidal stalk connecting the entire PCV complex with the underlying larger choroidal vessels. Pathological larger choroidal vessels called the pachy vessels in the outer Haller's layer have also been described.⁹²

OCTA also plays a role in managing the disease. Teo and colleagues⁹⁵ have reported that longitudinal OCTA shows a more significant reduction in lesion flow and pachy vessel size with combination therapy than monotherapy in PCV. The reduction in flow rates on OCTA shows up early as compared to the decrease in the subretinal fluid on OCT. Similarly, the residual linear flow in BVN is detectable even after therapy, although OCT may not show any subretinal fluid. This alerts the ophthalmologist to expect recurrences in the future.⁹⁵

Although OCTA assists in studying the anatomy and pathophysiology of PCV, there are potential disadvantages. Visualisation of pathology becomes difficult when there is an overlying haemorrhage or fluid. Further polyp detection rates are comparatively lesser as explained before. OCTA hence provides complementary information and must not be considered as a substitute for the gold standard ICGA in detecting and managing PCV.⁹⁴

Management

Figures 8–10 are shown in the following.

Medical management

Photodynamic therapy

Rationale of photodynamic therapy in PCV. Although a lot of work has been done on the role of photodynamic therapy (PDT) in PCV, the sequence of events leading to the resolution of the polyps is not clearly understood. PDT with verteporfin utilises selective endothelial uptake of photoactivated compound into PCV lesions.⁹⁶ Dilated choroidal vessels and interconnecting BVN may behave like CNV. PDT may cause selective thrombosis in polypoidal lesions and BVN, leading to resolution of exudation and haemorrhage from the lesions.⁹⁷ The smaller the vessel calibre and higher the deformity of vessels, more is the effect of PDT.⁹⁶ This may translate into a higher

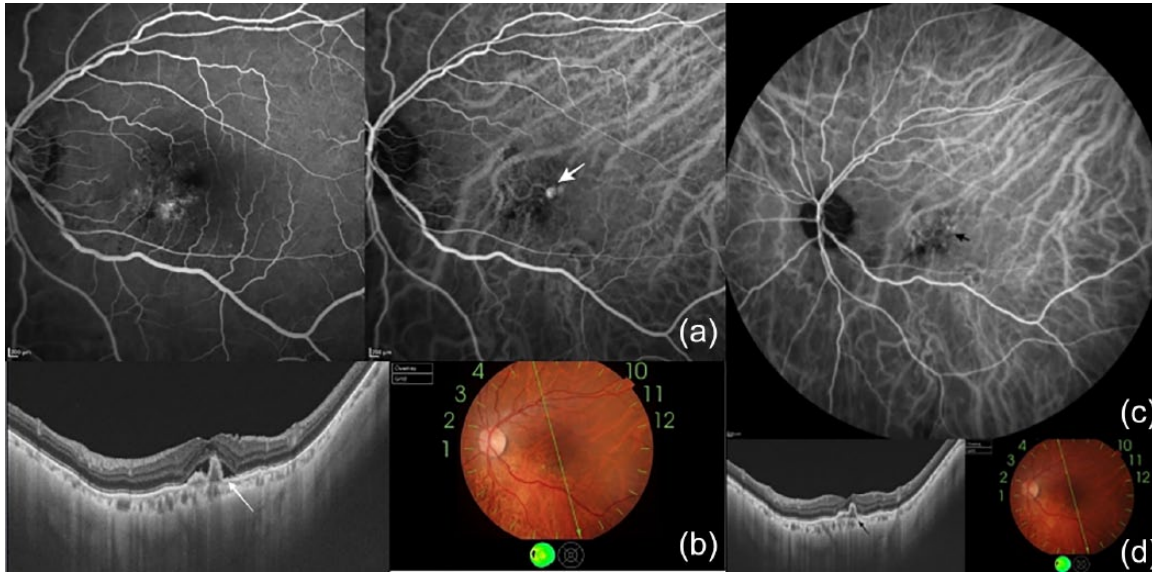


Figure 8. (a) Baseline fundus fluorescein angiography/indocyanine green angiography (FFA/ICG) images showing leak and late phase point hyperfluorescence (white arrow) due to the polyp. (b) Optical coherence tomography images showing pigment epithelial detachments (white arrow) characteristic of polypoidal choroidal vasculopathy – post combination therapy (photodynamic therapy + 3 doses of ranibizumab) resulted in (c) diminished visibility of the polyps on ICG and (d) reduced subretinal fluid on optical coherence tomography.

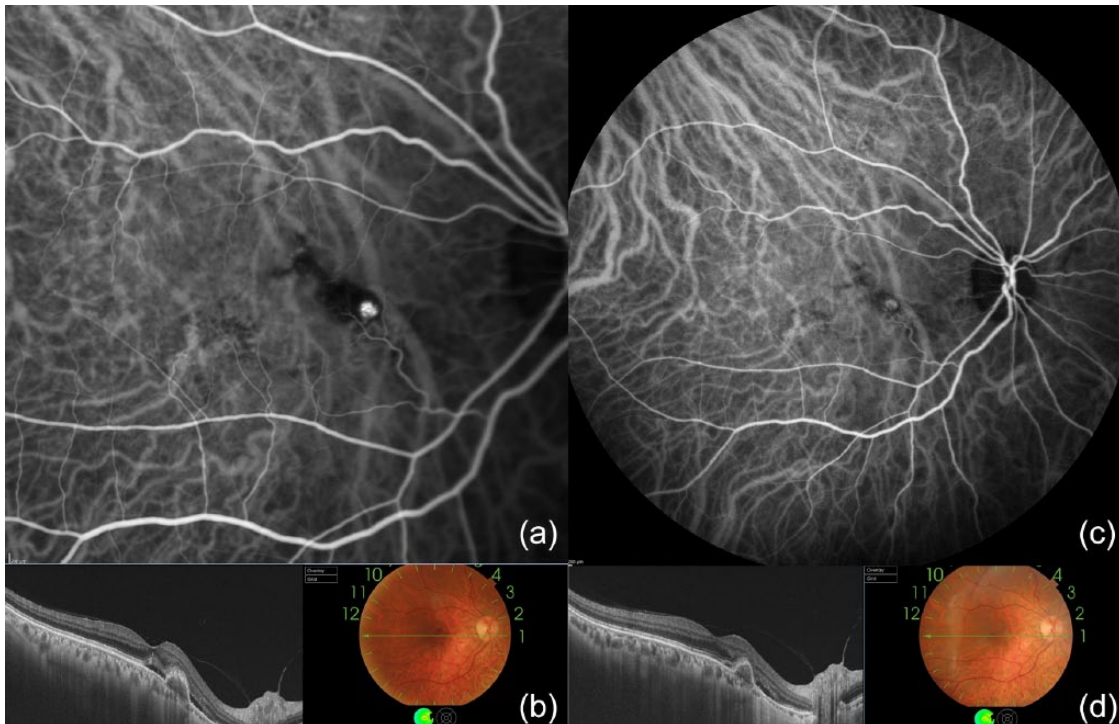


Figure 9. The other eye of the same patient mentioned in Figure 8 had developed (a) similar lesion of a single polyp on indocyanine green angiography (ICG). (b) The subretinal fluid and pigment epithelial detachment are evident on optical coherence tomography. Monotherapy with aflibercept (three monthly injections) caused (c) regression of polyps on ICG but (d) fluid persisted at the end of 3 months requiring rescue photodynamic therapy.

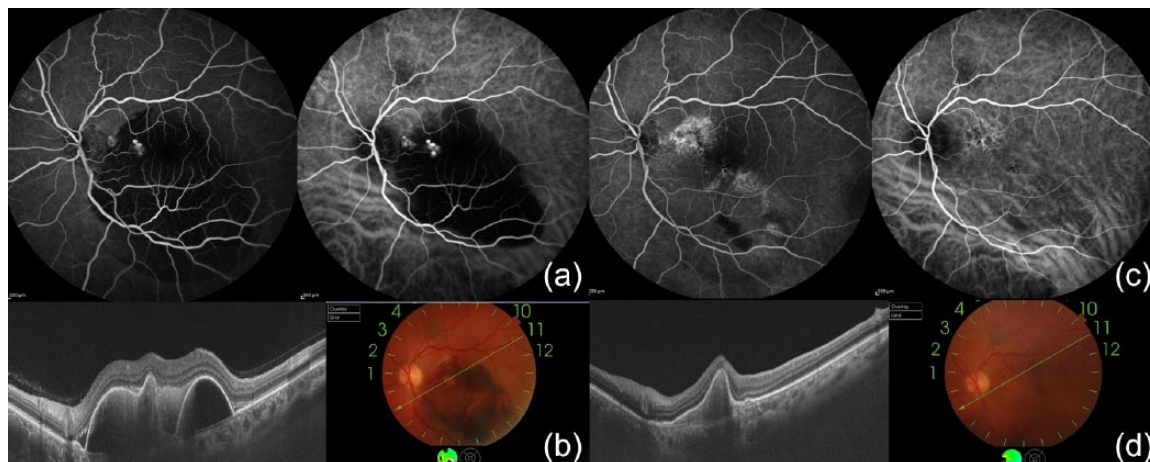


Figure 10. This patient presented with a massive submacular haemorrhage with (a) the cluster of polyps picked up on indocyanine angiography (ICG). (b) Swept source optical coherence tomography (SSOCT) showed subretinal bleed, both at subretinal and subretinal pigment epithelial levels. The patient underwent pars plana vitrectomy with subretinal injection of a therapeutic combination consisting of tissue plasminogen activator, bevacizumab and air. (c and d) Three months post-therapy, there was disappearance of polyps on ICG and reduction of submacular haemorrhage with residual scarring on SSOCT.

effect on polyps rather than BVN as these have smaller deformable vessels than BVN.

Mechanism of action. PDT uses a benzoporphyrin derivative, verteporfin which acts as a photosensitizer.⁹⁸ When injected intravenously, verteporfin gets concentrated in endothelial cells of abnormal choroidal vessels. Low-density lipoprotein receptors enhance the selective targeting of vascular endothelial cells.⁹⁸ Diode laser in the presence of verteporfin causes endothelial-bound intraluminal photo-thrombosis in these abnormal vessels. This leads to occlusion and subsequent resolution of exudation. Also, choroidal vascular remodelling has been reported to occur after PDT.⁹⁹ The lipoprotein receptors may not be absolutely essential for the action of PDT. Application of laser along with verteporfin may be enough to cause a non-selective temporary vascular occlusion in the choroidal vessels.¹⁰⁰ This would result in stagnant flow and thrombosis of the abnormal vessels.

Protocol for performing PDT in PCV. Baseline FFA, ICGA and OCTA (if available) are performed to determine the location and size of the lesions. The GLD of the lesion including the polyps and BVN is determined. The protocol followed is similar to that described in the treatment of AMD with PDT study.¹⁰¹

Repeat FFA and ICGA are performed 3 months after treatment to determine polyp and BVN

regression. PDT can be repeated if polyp regression is incomplete or recurrence of polyp occurs later on follow-up.

Visual and angiographic outcomes. Short term. Following PDT, abnormal choroidal vessels undergo remodelling, exudates get absorbed and polyps regress, leading to improvement in visual acuity. Stable or improved vision in the short term (up to 1 year) has been reported to be achieved in 80%–95% of cases in a majority of the studies.^{102–108} Mean visual improvement of 1.3–2.4 lines is reported in up to half of the cases.^{102–104} Mean treatment episodes in these studies ranged from 1.9/year to 2.9/year.

The short-term angiographic outcome is also favourable with PDT. Absence of FFA leakage was achieved in 74% and 91% eyes at 1 year as reported by Akaza and colleagues¹⁰⁵ and Chan and colleagues,¹⁰³ respectively. Complete regression of polyps has been attained in 78%–95% of the cases.^{103,105,106,108} However, BVN showed no to little change and persisted in a majority of eyes. Recurrence of polyps at the end of 1 year is uncommon and reported in up to 4.5%–5.7% eyes.^{103,105}

Long term. New or recurrent PCV lesions may develop during long-term follow-up. After 1 year, recurrence of polyps has been noted in 43.9%–77% eyes after PDT.^{104,109,110} In a prospective study of 43 eyes followed over 3 years by Akaza

and colleagues,¹¹⁰ BVN enlargement occurred in 55.8% eyes. In this study, all eyes had poorer final best corrected visual acuity (BCVA) as compared to baseline BCVA. This may be due to evolving retinal and RPE atrophy at the fovea from recurrent exudation. This highlights the need for long-term follow-up to detect early recurrence of PCV. Retreatment should be performed when symptoms worsen due to recurrence of polyps and subsequent exudation.

Complications. The most commonly reported complication of PDT for PCV is subretinal haemorrhage, estimated to be around 10%–30%.^{111–113} Hirami and colleagues¹¹¹ reported that most of the haemorrhage developed within 1 month of treatment. Despite this, the visual acuity was preserved in a majority of the eyes. Subretinal bleed can also breakthrough into the vitreous cavity and lead to a poorer outcome.^{111,112} Larger lesion size, larger laser spot size and leaking polyps are the common risk factors for post-PDT bleeding.¹¹¹ Other complications of full fluence PDT include massive suprachoroidal haemorrhage, RPE tears and micro rips, choroidal ischaemia, RPE atrophy, secondary CNV and fibrous scarring.^{60,114}

Alternative treatment protocols. Reduced fluence or half-dose PDT may be useful to prevent possible adverse effects of full fluence PDT.

Reduced fluence photodynamic therapy. Light energy of 25 J/cm² (instead of 50 J/cm²) is given for 83 s (300 mW/cm²) after 6 mg/m² verteporfin injection. A lower incidence of subretinal haemorrhage has been reported by Yamashita and colleagues¹¹⁵ and Sen and colleagues¹¹⁶ following reduced fluence photodynamic therapy (RFPDT), although PDT was combined with intravitreal anti-VEGF injection in these studies. On the other hand, a high rate of BVN persistence was reported by Ricci and colleagues¹¹⁷ with RFPDT.

Half-dose PDT. Dose of verteporfin is reduced to half (3 mg/m²) with a standard fluence of light energy (50 J/cm²). Wong and colleagues¹¹⁸ found that half-dose PDT along with ranibizumab was effective in treating solitary polyp cases but not in cases with BVN and/or multiple polyps.

Anti-VEGF agents

Role of VEGF in PCV. VEGF plays a vital role in the development of PCV. Its increased expression has

been found in the endothelial cells and RPE cells of excised CNV specimens in PCV eyes by Matsuoaka and colleagues.¹¹⁹ Also elevated levels of VEGF and pigment epithelium-derived factor (PEDF) have been found in aqueous samples of patients with active PCV by Tong and colleagues.³⁵ PEDF and VEGF may alter the formation of subfoveal CNV. Therefore, it is believed that anti-VEGF therapy may play a pioneering role in the treatment.

Effect of anti-VEGF therapy. The anti-permeability property of anti-VEGF agents probably plays a role in reducing the exudation from abnormal choroidal vessels and polyps, thereby decreasing the subretinal fluid and preserving vision.^{120–128} In most of the studies done for evaluating their role, three monthly injections were followed with as needed intravitreal anti-VEGF injection. Their safety and tolerability have been established in these studies with a variable follow-up, ranging from 3 months to 2 years.^{121,122,128} Anti-VEGF agents lead to resolution of subretinal haemorrhage, reduction in macular oedema and stabilisation of vision in 80%–100% of the eyes.^{120,124,127,128}

Limitations of anti-VEGF monotherapy. Polyps and BVN persist in a majority of eyes despite repeated injections of anti-VEGF agents. In short-term studies, Lai and colleagues¹²¹ and Kokame and colleagues¹²⁰ reported persistence of polyps in 100% eyes treated with bevacizumab and 67% eyes treated with ranibizumab, respectively. Chhablani and colleagues¹²⁴ reported persistence in 33% eyes treated with bevacizumab at 9 months follow-up. In a large prospective study done over 2 years using ranibizumab, Hikichi and colleagues¹²² found that polyp resolution occurred in 40% and 25% eyes at 1 year and 2 years, respectively. BVN on the other hand persisted in all eyes at 1 year and increased in size at 2-year follow-up.¹²²

While using aflibercept, Hosokawa and colleagues¹²⁶ reported polyp regression in 77% eyes at 6 months, which is higher than other anti-VEGF agents. In a large retrospective study over 1 year, Yamamoto and colleagues¹²⁷ noted polyp regression in 55% eyes but BVN regressed in size in only 13.4% eyes with aflibercept. In another retrospective study over 1-year duration, Hara and colleagues¹²⁸ noted polyp resolution in 66% eyes at 3 months and additional resolution in 13.8% eyes at 1 year with aflibercept. However, polyps recurred at 1 year in 26% eyes which had a

complete resolution at 3 months.¹²⁸ In a prospective study by Kokame and colleagues¹²⁹ with follow-up of 6 months, polyp regression was noted in 67% and BVN regression only in 4.8% eyes with aflibercept.

Incomplete regression of polyps was observed with the use of conbercept in PCV.¹³⁰ Complete regression was noted in only 56.5% of patients in the 0.5 mg group and 52.9% of those in the 2.0 mg group in this study.

From these studies, it can be extrapolated that if a suboptimal response to anti-VEGF therapy is found in eyes presumed to have AMD, the diagnosis should be reconsidered and PCV should be ruled out on ICGA.¹³¹

Choice of anti-VEGF treatment. No studies have proved the superiority of a particular anti-VEGF agent in PCV. Cho and colleagues¹³² did a retrospective review to compare the effect of intravitreal ranibizumab and bevacizumab in 121 PCV eyes followed till 12 months. They found no significant difference in visual improvement, reduction in central macular thickness (CMT) and regression of polyps between the groups. Polyps regressed only in 23.3% and 24.2% of eyes in ranibizumab and bevacizumab groups, respectively.

Aflibercept carries certain advantages over bevacizumab and ranibizumab like greater affinity for VEGF, longer half-life in the vitreous cavity and capacity to antagonise additional factors such as Placental growth factor (PGF). A few studies have examined the role of aflibercept in PCV patients who developed tachyphylaxis to ranibizumab and advocated switching to aflibercept in cases refractory to other agents.^{133,134}

Conbercept is the most recent anti-VEGF agent used in the management of PCV.¹³⁰ Similar to aflibercept, it also binds to all VEGF-A isoforms, PLGF and VEGF-B. But its affinity is higher than all other anti-VEGF agents. Safety and efficacy of both 0.5 and 2 mg dose of conbercept have been shown in a retrospective study of PCV patients from the landmark AURORA study.¹³⁰

Indications of anti-VEGF monotherapy. Anti-VEGF agents may be helpful in eyes with significant exudation and polyps with minimal or no activity.⁹⁷ They may also be considered in cases where polyps are not clearly visible in ICGA, and therefore, PDT cannot be undertaken. In these

cases, the polyps might be visualised in subsequent imaging after the subretinal fluid and/or macular haemorrhage resolves.

Combination therapy of PDT and anti-VEGF agents

Rationale of combination. The combination therapy uses together with the thrombotic property of PDT and anti-permeability property of anti-VEGF agents.⁷⁶ PDT may augment the action of anti-VEGF agents and help in the prevention of submacular haemorrhage by enhancing polyp regression.

Effect of combination therapy. Numerous studies have found superior results with combination therapy than monotherapy alone.^{85,121,135-138} The landmark study among these is EVEREST study, a randomised control trial (RCT) of 61 symptomatic treatment-naïve PCV cases subjected to one of the three treatment arms: PDT monotherapy, ranibizumab monotherapy or a combination of both. The polyp regression was greater in the combination therapy and PDT monotherapy groups as compared to the ranibizumab monotherapy group at 6 months (77.8% versus 71.4% versus 28.6%, respectively).⁸⁵ Also, the combination therapy had most favourable BCVA and retinal thickness at 6 months.

In a retrospective study of 146 PCV eyes by Gomi and colleagues,¹³⁵ polyp resolution and recurrence rates were similar with combined PDT and bevacizumab treatment compared with PDT monotherapy. But, the combined therapy group had significantly rapid visual recovery and superior final visual outcome than the monotherapy group at all visits till 12 months. In another retrospective study comparing combination therapy with ranibizumab monotherapy in 57 cases by Saito and colleagues,¹³⁷ combination group had better vision gain at 2 years as compared to PDT alone (+2.63 line versus -0.16 lines). Combined therapy group did not develop any subretinal haemorrhage compared to 25% patients in the PDT group. Combination therapy also decreased the requirement of PDT over 24 months as compared to PDT alone (1.4 versus 2.6 sessions).

To overcome the limitation of EVEREST study (smaller follow-up and a limited number of eyes, $n = 61$ eyes), EVEREST II was undertaken.¹³⁹ In this large multicentre trial of 322 Asian individuals, treatment with ranibizumab plus PDT resulted in greater BCVA gain (8.3 versus

5.1 letters) than ranibizumab monotherapy and complete resolution of lesions with fewer injections at 12 months of follow-up. The combination therapy was not only non-inferior but was superior to the monotherapy group.

However, the potential benefit of adding PDT was not found by the landmark PLANET trial while using Aflibercept.¹⁴⁰ The PLANET study evaluated the safety and efficacy of intravitreal aflibercept injection (IAI) in participants with PCV and compared monotherapy *versus* combination therapy with rescue PDT. Monotherapy was non-inferior to IAI/PDT in terms of the need for PDT rescue therapy. The BCVA gains and the decrease in CMT were similar in both the groups. At 52 weeks, nearly 40% of the cases had regression of polypoidal lesions on ICGA in both the groups. Polyp activity was not seen in greater than 80% of the patients at week 52 in both the groups.

Limitations of combination therapy. The advantages of combination treatment are momentary. The visual gain diminishes after 6 months to 1 year and the final visual acuity at 2 years is not statistically different from the baseline.^{141–143} It is possible that if PDT is applied days after the anti-VEGF injection (half-life of the drug), the collegial benefit of the combined treatment may be limited.

The combined therapy does not fare well in terms of visual gain in already treated eyes with PDT. In a study of 27 cases who had received PDT monotherapy before combination treatment, Tomita and colleagues¹⁴⁴ reported that the mean BCVA deteriorated from baseline at 12 months. BVN tends to persist following combination treatment as well. BVN may also enlarge and develop polyps at their terminal ends despite treatment.¹⁴⁵

Variable drugs and protocols have been used for combination therapy in the majority of the studies, and the standard approach is lacking. RFPDT may overcome the adverse effects of full fluence PDT as seen in a few small case series.^{146,147} In this regard, large RCT needs to be done to evaluate the non-inferiority and/or benefits of RFPDT over full fluence Photodynamic therapy (FFPDT).

Comparison of PDT and anti-VEGF therapy

EVEREST study. The landmark EVEREST study found superiority of PDT in attaining regression of polyps as compared to intravitreal ranibizumab (71.4% *versus* 28.6%; $p < 0.01$).⁸⁵ Although the

visual gain was better in the injection group than in the PDT group, statistical significance was not achieved [mean change in BCVA, 7.5 ± 10.6 (PDT) and 9.2 ± 12.4 (ranibizumab)].

LAPTOP study. As the visual outcomes were not significantly superior with any particular treatment group in the EVEREST study, LAPTOP study was performed to address this issue. It was a prospective multicenter RCT of 93 treatment-naïve PCV patients comparing PDT *versus* ranibizumab. At 12 months, the injection group had superior visual gains as compared to the PDT monotherapy group.¹¹² In PDT arm, 17.0% achieved visual acuity gain, 55.3% had no change and 27.7% had visual acuity loss. These were 30.4%, 60.9% and 8.7%, respectively, in the ranibizumab arm, significantly better than the PDT arm ($p = 0.039$). The retinal thickness was reduced significantly in both the groups. The results were reciprocated at 24 months as well.¹⁴⁸

From these studies, it can be concluded that although PDT can efficiently induce regression of polypoidal lesions, the same may not be implied to the visual outcome. Monthly injections of ranibizumab followed by pro re nata (PRN) treatment provide superior visual gains than PDT alone.

Thermal laser photocoagulation

Laser photocoagulation has been used for extrafoveal symptomatic PCV in several studies.^{12,149,150} These studies have used either 514 nm argon green laser or 532 nm diode laser or 532 nm neodymium-doped yttrium aluminium garnet (Nd:YAG) laser. The polyps, as well as the BVN, can be directly targeted. Feeder vessel identification on ICG video-angiography can help in precise target identification and treatment.¹⁵¹ Significant visual improvement is reported with near complete regression of peripapillary polyps and significant regression in macular polyps.¹²

However, a chorioretinal scar forms in the laser-treated area and manifests as a scotoma. Additional limitations are recurrent or persistent exudation from the polyps, RPE tears, worsening of or development of new haemorrhage (subretinal or sub-RPE) and formation of secondary CNV.

Triamcinolone acetonide

Triamcinolone acetonide (TA) has been used in the treatment of PCV either in the form of an

intravitreal injection or in the form of subtenon depot.^{152–155} TA probably decreases the polyp size and exudation. It also decreases the severity of choriocapillaris occlusion if used along with PDT.¹⁵³ Following trans-tenon retrobulbar injections of 12 mg TA, Okubo and colleagues¹⁵² noted a reduction in the size of the polyp and complete resolution of subretinal fluid. In a comparative study on PDT monotherapy *versus* combination triple therapy (PDT, intravitreal bevacizumab and intravitreal TA), Nakata and colleagues¹⁵⁴ reported visual improvement in a significantly greater percentage of eyes in the combination group at 2 years (41.7% *versus* 12.5%). The retreatment rates and post-treatment vitreous haemorrhage were less in the combination group. Contrary to this, Lai and colleagues¹⁵⁵ reported increased cataract development and rise in intraocular pressure with no visual gain in PCV eyes treated with intravitreal TA in addition to PDT. Therefore, till further large-scale studies demonstrate its efficacy and safety in PCV, the routine use of TA is not advocated.

Surgical management for submacular haemorrhage

PCV often presents with recurrent extensive submacular haemorrhage.¹⁵⁶ Subretinal or sub-RPE blood damages the retinal photoreceptors by nutritional deprivation, iron toxicity and mechanical shearing effect.¹⁵⁶ Hence, its early removal is justified to prevent permanent visual loss.

There are multiple options for management of massive submacular haemorrhage (>4 disc area) in PCV. However, there is still no consensus regarding the best approach with the least risk of complication. Published techniques in the literature include pneumatic displacement with intravitreal gas alone or in combination with adjuncts like intravitreal recombinant tissue plasminogen activator (rtPA)/anti-VEGF agent.^{156–158}

Pneumatic displacement can be tried within 10–14 days of onset of bleed. Either sulphur hexafluoride (SF₆) or perfluoropropane (C₃F₈) gas can be used for this purpose followed by prone position for a few days. Not only does intravitreal gas displace the subretinal bleed, but it also hastens the absorption of sub-RPE bleed by pressure effect.¹⁵⁸ The bleed gets displaced in 1 or 2 weeks usually, and then an FFA/ICGA can then be performed. Thrombosed polypoidal lesions do not require further treatment and patient can be

monitored for resolution of bleed. However, if leakage is present in the presence of active polypoidal lesions, PDT can be performed with or without additional anti-VEGF treatment.

Chan and colleagues¹⁵⁶ did an interventional study of six PCV eyes with submacular bleed, wherein the bleed was displaced with 100% C₃F₈ (0.4 mL) injected into the vitreous cavity. This was later followed with PDT treatment at 1–2 weeks. A moderate visual gain was obtained in all patients with the displacement of bleed. No serious complications were noted at 1 year. Nayak and colleagues¹⁵⁸ combined intravitreal bevacizumab injection to pneumatic displacement in three eyes with PCV-related massive subretinal and sub-RPE bleed and found that even sub-RPE bleed resolved with treatment. Intravitreal rtPA (50–100 µg) is believed to liquefy the subretinal clot and help in the displacement of bleed.¹⁵⁷

Vitreous haemorrhage develops commonly in PCV patients after pneumatic displacement and intravitreal injection of rtPA.¹⁵⁹ Other complications of the procedure include a rise in intraocular pressure, lenticular changes, and risk of infection, retinal break, and rhegmatogenous retinal detachment.

Existing literature on the role of vitrectomy for subretinal bleed in PCV is scarce.^{160–162} Pars plana vitrectomy with a subretinal administration of rtPA (50 µg) and pneumatic displacement by intravitreal gas with short-term facedown positioning can help in near complete displacement and resolution of submacular bleeds. Furthermore, it also allows early treatment of the polypoidal lesions by PDT with or without anti-VEGF injection. In a prospective study of 20 PCV cases with submacular haemorrhage, who received either subretinal tissue plasminogen activator (tPA) with vitrectomy or intravitreal injection of tPA and gas, visual and anatomical results were better in the vitrectomy arm.¹⁶² Vitrectomy may also be needed in cases with breakthrough vitreous haemorrhage, which may be *de novo* or following intervention like PDT/pneumatic displacement.

The technique of vitrectomy, subretinal rtPA injection and pneumatic displacement was described by Hauptert and colleagues¹⁶³ for wet AMD cases. However, this technique aims at the sequential treatment of the disease. Once the bleed clears, the underlying disease pathology is then targeted with anti-VEGF therapy. Martel

and Mahmoud¹⁶⁴ tailored this technique with subretinal injection of rtPA (0.4 mL of 12.5 µg/0.1 mL concentration) along with bevacizumab and air. The subretinal air decreases the buoyancy of bleed which facilitates its displacement and bevacizumab targets the underlying pathology directly and simultaneously.

To conclude, PCV is an entity distinct from AMD in many domains, with characteristic genotype, pathophysiology and immunological traits. The treatment differs from that of AMD and is often guided by the angiographic type of disease and symptoms of the patient. However, there are many limitations in the understanding of the disease due to its heterogeneity in the clinical features and treatment outcomes. Future studies are warranted to further characterise the immune-mediated inflammation in PCV. Given the enormous morbidity with the disease, the targets of primary and secondary prevention need to be explored. Meanwhile, the existing treatment protocols need to be refined in view of emerging complications of the treatment and recurrence of the disease.

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References

1. Stern RM, Zakov ZN, Zegarra H, *et al.* Multiple recurrent serosanguineous retinal pigment epithelial detachments in black women. *Am J Ophthalmol* 1985; 100: 560–569.
2. Yannuzzi LA, Sorenson J, Spaide RF, *et al.* Idiopathic polypoidal choroidal vasculopathy (IPCVC). *Retina* 1990; 10: 1–8.
3. Kleiner RC, Brucker AJ and Johnson RL. Posterior uveal bleeding syndrome. *Ophthalmology* 1984; 94: 110.
4. Kleiner RC, Brucker AJ and Johnston RL. The posterior uveal bleeding syndrome. *Retina* 1990; 10: 9–17.
5. Yannuzzi LA, Ciardella A, Spaide RF, *et al.* The expanding clinical spectrum of idiopathic polypoidal choroidal vasculopathy. *Arch Ophthalmol* 1997; 115: 478–485.
6. Yannuzzi LA, Wong DW, Sforzolini BS, *et al.* Polypoidal choroidal vasculopathy and neovascularized age-related macular degeneration. *Arch Ophthalmol* 1999; 117: 1503–1510.
7. Yannuzzi LA, Freund KB, Goldbaum M, *et al.* Polypoidal choroidal vasculopathy masquerading as central serous chorioretinopathy. *Ophthalmology* 2000; 107: 767–777.
8. Gass JDM. Multifocal idiopathic sub RPE neovascularization occurring in darkly pigmented individuals. In: *Stereoscopic Atlas of Macular Diseases*. St. Louis, MO: Mosby, 1997, p. 250.
9. Yannuzzi LA, Nogueira FB, Spaide RF, *et al.* Idiopathic polypoidal choroidal vasculopathy: a peripheral lesion. *Arch Ophthalmol* 1998; 116: 382–383.
10. Moorthy RS, Lyon AT, Rabb MF, *et al.* Idiopathic polypoidal choroidal vasculopathy of the macula. *Ophthalmology* 1998; 105: 1380–1385.
11. Uyama M, Matsubara T, Fukushima I, *et al.* Idiopathic polypoidal choroidal vasculopathy in Japanese patients. *Arch Ophthalmol* 1999; 117: 1035–1042.
12. Lafaut BA, Leys AM, Snyers B, *et al.* Polypoidal choroidal vasculopathy in Caucasians. *Graefes Arch Clin Exp Ophthalmol* 2000; 238: 752–759.
13. Ahuja RM, Stanga PE, Vingerling JR, *et al.* Polypoidal choroidal vasculopathy in exudative and haemorrhagic pigment epithelial detachments. *Br J Ophthalmol* 2000; 84: 479–484.
14. Coscas G, Lupidi M, Coscas F, *et al.* Toward a specific classification of polypoidal choroidal vasculopathy: idiopathic disease or subtype of age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2015; 56: 3187–3195.
15. Lafaut BA, Aisenbrey S, VandenBroecke C, *et al.* Polypoidal choroidal vasculopathy pattern in age-related macular degeneration: a clinicopathologic correlation. *Retina* 2000; 20: 650–654.
16. MacCumber MW, Dastgheib K, Bressler NM, *et al.* Clinicopathologic correlation of the multiple recurrent serosanguineous retinal pigment epithelial detachments syndrome. *Retina* 1994; 14: 143–152.

17. Okubo A, Sameshima M, Uemura A, *et al.* Clinicopathological correlation of polypoidal choroidal vasculopathy revealed by ultrastructural study. *Br J Ophthalmol* 2002; 86: 1093–1098.
18. Nakashizuka H, Mitsumata M, Okisaka S, *et al.* Clinicopathologic findings in polypoidal choroidal vasculopathy. *Invest Ophthalmol Vis Sci* 2008; 49: 4729–4737.
19. Yuzawa M, Mori R and Kawamura A. The origins of polypoidal choroidal vasculopathy. *Br J Ophthalmol* 2005; 89: 602–607.
20. Ciardella AP, Donsoff IM, Huang SJ, *et al.* Polypoidal choroidal vasculopathy. *Surv Ophthalmol* 2004; 49: 25–37.
21. Kumar S, Nakashizuka H, Jones A, *et al.* Proteolytic degradation and inflammation play critical roles in polypoidal choroidal vasculopathy. *Am J Pathol* 2017; 187: 2841–2857.
22. Subhi Y, Krogh Nielsen M, Molbech CR, *et al.* CD11b and CD200 on circulating monocytes differentiate two angiographic subtypes of polypoidal choroidal vasculopathy. *Invest Ophthalmol Vis Sci* 2017; 58: 5242–5250.
23. Subhi Y, Krogh Nielsen M, Molbech CR, *et al.* Altered proportion of CCR2+ and CX3CR1+ circulating monocytes in neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. *Clin Exp Ophthalmol* 2018; 46: 661–669.
24. Subhi Y, Nielsen MK, Molbech CR, *et al.* T-cell differentiation and CD56+ levels in polypoidal choroidal vasculopathy and neovascular age-related macular degeneration. *Aging* 2017; 9: 2436–2452.
25. Chen H, Liu K, Chen LJ, *et al.* Genetic associations in polypoidal choroidal vasculopathy: a systematic review and meta-analysis. *Mol Vis* 2012; 18: 816–829.
26. Huang L, Zhang H, Cheng C-Y, *et al.* A missense variant in FGD6 confers increased risk of polypoidal choroidal vasculopathy. *Nat Genet* 2016; 48: 640–647.
27. Ueta T, Obata R, Inoue Y, *et al.* Background comparison of typical age-related macular degeneration and polypoidal choroidal vasculopathy in Japanese patients. *Ophthalmology* 2009; 116: 2400–2406.
28. Sakurada Y, Yoneyama S, Imasawa M, *et al.* Systemic risk factors associated with polypoidal choroidal vasculopathy and neovascular age-related macular degeneration. *Retina* 2013; 33: 841–845.
29. Cackett P, Yeo I, Cheung CMG, *et al.* Relationship of smoking and cardiovascular risk factors with polypoidal choroidal vasculopathy and age-related macular degeneration in Chinese persons. *Ophthalmology* 2011; 118: 846–852.
30. Friedman E, Smith TR, Kuwabara T, *et al.* Choroidal vascular patterns in hypertension. *Arch Ophthalmol* 1964; 71: 842–850.
31. Lip PL, Hope-Ross MW and Gibson JM. Idiopathic polypoidal choroidal vasculopathy: a disease with diverse clinical spectrum and systemic associations. *Eye* 2000; 14: 695–700.
32. Grover DP. Obstructive sleep apnea and ocular disorders. *Curr Opin Ophthalmol* 2010; 21: 454–458.
33. Kubisz P, Chudy P, Stasko J, *et al.* Circulating vascular endothelial growth factor in the normo- and/or microalbuminuric patients with type 2 diabetes mellitus. *Acta Diabetol* 2010; 47: 119–124.
34. Mahdy RA, Nada WM, Hadhoud KM, *et al.* The role of vascular endothelial growth factor in the progression of diabetic vascular complications. *Eye* 2010; 24: 1576–1584.
35. Tong J-P, Chan W-M, Liu DTL, *et al.* Aqueous humor levels of vascular endothelial growth factor and pigment epithelium-derived factor in polypoidal choroidal vasculopathy and choroidal neovascularization. *Am J Ophthalmol* 2006; 141: 456–462.
36. Rishi P, Rishi E, Mathur G, *et al.* Ocular perfusion pressure and choroidal thickness in eyes with polypoidal choroidal vasculopathy, wet-age-related macular degeneration, and normals. *Eye* 2013; 27: 1038–1043.
37. Park HS and Kim IT. Clinical characteristics of polypoidal choroidal vasculopathy associated with chronic central serous chorioretinopathy. *Korean J Ophthalmol* 2012; 26: 15–20.
38. Ahuja RM, Downes SM, Stanga PE, *et al.* Polypoidal choroidal vasculopathy and central serous chorioretinopathy. *Ophthalmology* 2001; 108: 1009–1010.
39. Koizumi H, Yamagishi T, Yamazaki T, *et al.* Relationship between clinical characteristics of polypoidal choroidal vasculopathy and choroidal vascular hyperpermeability. *Am J Ophthalmol* 2013; 155: 305.e1–313.e1.
40. Jirarattanasopa P, Ooto S, Tsujikawa A, *et al.* Assessment of macular choroidal thickness by optical coherence tomography and angiographic

- changes in central serous chorioretinopathy. *Ophthalmology* 2012; 119: 1666–1678.
41. Kauppinen A, Paterno JJ, Blasiak J, *et al.* Inflammation and its role in age-related macular degeneration. *Cell Mol Life Sci* 2016; 73: 1765–1786.
 42. Cheng H-C, Liu J-H, Lee S-M, *et al.* Hyperhomocysteinemia in patients with polypoidal choroidal vasculopathy: a case control study. *PLoS ONE* 2014; 9: e110818.
 43. Kikuchi M, Nakamura M, Ishikawa K, *et al.* Elevated C-reactive protein levels in patients with polypoidal choroidal vasculopathy and patients with neovascular age-related macular degeneration. *Ophthalmology* 2007; 114: 1722–1727.
 44. Subhi Y, Krogh Nielsen M, Molbech CR, *et al.* Plasma markers of chronic low-grade inflammation in polypoidal choroidal vasculopathy and neovascular age-related macular degeneration. *Acta Ophthalmol* 2019; 97: 99–106.
 45. McCully KS. Chemical pathology of homocysteine. IV. Excitotoxicity, oxidative stress, endothelial dysfunction, and inflammation. *Ann Clin Lab Sci* 2009; 39: 219–232.
 46. Zeng R, Wen F, Zhang X, *et al.* Serum levels of matrix metalloproteinase 2 and matrix metalloproteinase 9 elevated in polypoidal choroidal vasculopathy but not in age-related macular degeneration. *Mol Vis* 2013; 19: 729–736.
 47. Jones A, Kumar S, Zhang N, *et al.* Increased expression of multifunctional serine protease, HTRA1, in retinal pigment epithelium induces polypoidal choroidal vasculopathy in mice. *Proc Natl Acad Sci U S A* 2011; 108: 14578–14583.
 48. Lorentzen TD, Subhi Y and Sørensen TL. Presenting characteristics and prevalence of polypoidal choroidal vasculopathy in Scandinavian patients with treatment-naïve exudative age-related macular degeneration. *Acta Ophthalmol* 2018; 96: 475–480.
 49. Scassellati-Sforzolini B, Mariotti C, Bryan R, *et al.* Polypoidal choroidal vasculopathy in Italy. *Retina* 2001; 21: 121–125.
 50. Yadav S, Parry DG, Beare NAV, *et al.* Polypoidal choroidal vasculopathy: a common type of neovascular age-related macular degeneration in Caucasians. *Br J Ophthalmol* 2017; 101: 1377–1380.
 51. Ladas ID, Rouvas AA, Moschos MM, *et al.* Polypoidal choroidal vasculopathy and exudative age-related macular degeneration in Greek population. *Eye* 2004; 18: 455–459.
 52. Sho K, Takahashi K, Yamada H, *et al.* Polypoidal choroidal vasculopathy: incidence, demographic features, and clinical characteristics. *Arch Ophthalmol* 2003; 121: 1392–1396.
 53. Tao Y, Hu J and Li XX. Clinical characteristics of 254 cases of polypoidal choroidal vasculopathy. *Chinese J Ocular Fundus Dis* 2012; 28: 4.
 54. Byeon SH, Lee SC, Oh H-S, *et al.* Incidence and clinical patterns of polypoidal choroidal vasculopathy in Korean patients. *Jpn J Ophthalmol* 2008; 52: 57–62.
 55. Hou J, Tao Y, Li X, *et al.* Clinical characteristics of polypoidal choroidal vasculopathy in Chinese patients. *Graefes Arch Clin Exp Ophthalmol* 2011; 249: 975–979.
 56. Lorentzen TD, Subhi Y and Sørensen TL. Prevalence of polypoidal choroidal vasculopathy in white patients with exudative age-related macular degeneration: systematic review and meta-analysis. *Retina* 2018; 38: 2363–2371.
 57. Anantharaman G, Ramkumar G, Gopalakrishnan M, *et al.* Clinical features, management and visual outcome of polypoidal choroidal vasculopathy in Indian patients. *Indian J Ophthalmol* 2010; 58: 399–405.
 58. Honda S, Matsumiya W and Negi A. Polypoidal choroidal vasculopathy: clinical features and genetic predisposition. *Ophthalmologica* 2014; 231: 59–74.
 59. Uyama M, Wada M, Nagai Y, *et al.* Polypoidal choroidal vasculopathy: natural history. *Am J Ophthalmol* 2002; 133: 639–648.
 60. Musashi K, Tsujikawa A, Hiramami Y, *et al.* Microrips of the retinal pigment epithelium in polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2007; 143: 883–885.
 61. Iwama D, Tsujikawa A, Sasahara M, *et al.* Polypoidal choroidal vasculopathy with drusen. *Jpn J Ophthalmol* 2008; 52: 116–121.
 62. Imamura Y, Engelbert M, Iida T, *et al.* Polypoidal choroidal vasculopathy: a review. *Surv Ophthalmol* 2010; 55: 501–515.
 63. Bhoombunchoo C, Yospaiboon Y, Thoongsuwan S, *et al.* Idiopathic polypoidal choroidal vasculopathy in Thai patients with clinical and angiographic choroidal neovascularization. *Clin Ophthalmol* 2017; 11: 317–322.

64. Goldman DR, Freund KB, McCannel CA, *et al.* Peripheral polypoidal choroidal vasculopathy as a cause of peripheral exudative hemorrhagic chorioretinopathy: a report of 10 eyes. *Retina* 2013; 33: 48–55.
65. Shields CL, Salazar PF, Mashayekhi A, *et al.* Peripheral exudative hemorrhagic chorioretinopathy simulating choroidal melanoma in 173 eyes. *Ophthalmology* 2009; 116: 529–535.
66. Gharehbagh SS, Subhi Y and Sorensen TL. Efficacy of aflibercept for polypoidal choroidal vasculopathy in Caucasians. *Acta Ophthalmol* 2018; 96: e94–e95.
67. Yamaoka S, Okada AA, Sugahara M, *et al.* Clinical features of polypoidal choroidal vasculopathy and visual outcomes in the absence of classic choroidal neovascularization. *Ophthalmologica* 2010; 224: 147–152.
68. Kim JH, Chang YS, Kim JW, *et al.* Submacular hemorrhage and grape-like polyp clusters: factors associated with reactivation of the lesion in polypoidal choroidal vasculopathy. *Eye* 2017; 31: 1678–1684.
69. Cheung CMG, Yang E, Lee WK, *et al.* The natural history of polypoidal choroidal vasculopathy: a multi-center series of untreated Asian patients. *Graefes Arch Clin Exp Ophthalmol* 2015; 253: 2075–2085.
70. Alshahrani ST, Al Shamsi HN, Kahtani ES, *et al.* Spectral-domain optical coherence tomography findings in polypoidal choroidal vasculopathy suggest a type 1 neovascular growth pattern. *Clin Ophthalmol* 2014; 8: 1689–1695.
71. Iijima H, Imai M, Gohdo T, *et al.* Optical coherence tomography of idiopathic polypoidal choroidal vasculopathy. *Am J Ophthalmol* 1999; 127: 301–305.
72. Iijima H, Iida T, Imai M, *et al.* Optical coherence tomography of orange-red subretinal lesions in eyes with idiopathic polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2000; 129: 21–26.
73. Sato T, Kishi S, Watanabe G, *et al.* Tomographic features of branching vascular networks in polypoidal choroidal vasculopathy. *Retina* 2007; 27: 589–594.
74. De Salvo G, Vaz-Pereira S, Keane PA, *et al.* Sensitivity and specificity of spectral-domain optical coherence tomography in detecting idiopathic polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2014; 158: 1228.e1–1238.e1.
75. Liu R, Li J, Li Z, *et al.* Distinguishing polypoidal choroidal vasculopathy from typical neovascular age-related macular degeneration based on spectral domain optical coherence tomography. *Retina* 2016; 36: 778–786.
76. Koh AHC, Chen LJ, Chen SJ, *et al.* Polypoidal choroidal vasculopathy: evidence-based guidelines for clinical diagnosis and treatment. *Retina* 2013; 33: 686–716.
77. Chhablani J and Barteselli G. Clinical applications of choroidal imaging technologies. *Indian J Ophthalmol* 2015; 63: 384–390.
78. Yang LH, Jonas JB and Wei WB. Optical coherence tomographic enhanced depth imaging of polypoidal choroidal vasculopathy. *Retina* 2013; 33: 1584–1589.
79. Lim TH, Laude A and Tan CSH. Polypoidal choroidal vasculopathy: an angiographic discussion. *Eye* 2010; 24: 483–490.
80. Squirrel DM, Bacon JF and Brand CS. To investigate the prevalence of polypoidal choroidal vasculopathy in presumed age-related peripapillary subretinal neovascular membranes. *Clin Exp Ophthalmol* 2009; 37: 368–372.
81. Gomi F, Sawa M, Mitarai K, *et al.* Angiographic lesion of polypoidal choroidal vasculopathy on indocyanine green and fluorescein angiography. *Graefes Arch Clin Exp Ophthalmol* 2007; 245: 1421–1427.
82. Tan CSH, Ngo WK, Lim LW, *et al.* A novel classification of the vascular patterns of polypoidal choroidal vasculopathy and its relation to clinical outcomes. *Br J Ophthalmol* 2014; 98: 1528–1533.
83. Japanese Study Group of Polypoidal Choroidal Vasculopathy. Criteria for diagnosis of polypoidal choroidal vasculopathy. *Nippon Ganka Gakkai Zasshi* 2005; 109: 417–427.
84. Kwok AKH, Lai TYY, Chan CWN, *et al.* Polypoidal choroidal vasculopathy in Chinese patients. *Br J Ophthalmol* 2002; 86: 892–897.
85. Koh A, Lee WK, Chen L-J, *et al.* EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy. *Retina* 2012; 32: 1453–1464.
86. Cackett P, Wong D and Yeo I. A classification system for polypoidal choroidal vasculopathy. *Retina* 2009; 29: 187–191.
87. Tomiyasu T, Nozaki M, Yoshida M, *et al.* Characteristics of polypoidal choroidal vasculopathy evaluated by optical coherence

- tomography angiography. *Invest Ophthalmol Vis Sci* 2016; 57: OCT324–OCT330.
88. Spaide RF, Yannuzzi LA, Slakter JS, *et al.* Indocyanine green videoangiography of idiopathic polypoidal choroidal vasculopathy. *Retina* 1995; 15: 100–110.
 89. Wang M, Zhou Y, Gao SS, *et al.* Evaluating polypoidal choroidal vasculopathy with optical coherence tomography angiography. *Invest Ophthalmol Vis Sci* 2016; 57: OCT526–OT532.
 90. De Carlo TE, Romano A, Waheed NK, *et al.* A review of optical coherence tomography angiography (OCTA). *Int J Retina Vitreol* 2015; 1: 5.
 91. Takayama K, Ito Y, Kaneko H, *et al.* Comparison of indocyanine green angiography and optical coherence tomographic angiography in polypoidal choroidal vasculopathy. *Eye* 2017; 31: 45–52.
 92. Chi Y-T, Yang C-H and Cheng C-K. Optical coherence tomography angiography for assessment of the 3-dimensional structures of polypoidal choroidal vasculopathy. *JAMA Ophthalmol* 2017; 135: 1310–1316.
 93. Chan SY, Wang Q, Wang YX, *et al.* Polypoidal choroidal vasculopathy upon optical coherence tomographic angiography. *Retina* 2018; 38: 1187–1194.
 94. Inoue M, Balaratnasingam C and Freund KB. Optical coherence tomography angiography of polypoidal choroidal vasculopathy and polypoidal choroidal neovascularization. *Retina* 2015; 35: 2265–2274.
 95. Teo KYC, Yanagi Y, Lee SY, *et al.* Comparison of optical coherence tomography angiographic changes after anti-vascular endothelial growth factor therapy alone or in combination with photodynamic therapy in polypoidal choroidal vasculopathy. *Retina* 2018; 38: 1675–1687.
 96. Chan W-M, Lai TYY, Tano Y, *et al.* Photodynamic therapy in macular diseases of Asian populations: when East meets West. *Jpn J Ophthalmol* 2006; 50: 161–169.
 97. Lai TYY and Chan W-M. An update in laser and pharmaceutical treatment for polypoidal choroidal vasculopathy. *Asia Pac J Ophthalmol* 2012; 1: 97–104.
 98. Schmidt-Erfurth U, Hasan T, Gragoudas E, *et al.* Vascular targeting in photodynamic occlusion of subretinal vessels. *Ophthalmology* 1994; 101: 1953–1961.
 99. Chan W-M, Lam DSC, Lai TYY, *et al.* Choroidal vascular remodelling in central serous chorioretinopathy after indocyanine green guided photodynamic therapy with verteporfin: a novel treatment at the primary disease level. *Br J Ophthalmol* 2003; 87: 1453–1458.
 100. Schlötzer-Schrehardt U, Viestenz A, Naumann GO, *et al.* Dose-related structural effects of photodynamic therapy on choroidal and retinal structures of human eyes. *Graefes Arch Clin Exp Ophthalmol* 2002; 240: 748–757.
 101. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials – TAP report. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group. *Arch Ophthalmol* 1999; 117: 1329–1345.
 102. Spaide RF, Donsoff I, Lam DL, *et al.* Treatment of polypoidal choroidal vasculopathy with photodynamic therapy. *Retina* 2012; 32(Suppl. 1): 529–535.
 103. Chan W-M, Lam DSC, Lai TYY, *et al.* Photodynamic therapy with verteporfin for symptomatic polypoidal choroidal vasculopathy: one-year results of a prospective case series. *Ophthalmology* 2004; 111: 1576–1584.
 104. Silva RM, Figueira J, Cachulo ML, *et al.* Polypoidal choroidal vasculopathy and photodynamic therapy with verteporfin. *Graefes Arch Clin Exp Ophthalmol* 2005; 243: 973–979.
 105. Akaza E, Yuzawa M, Matsumoto Y, *et al.* Role of photodynamic therapy in polypoidal choroidal vasculopathy. *Jpn J Ophthalmol* 2007; 51: 270–277.
 106. Otani A, Sasahara M, Yodoi Y, *et al.* Indocyanine green angiography: guided photodynamic therapy for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2007; 144: 7–14.
 107. Lee M-W, Yeo I, Wong D, *et al.* Photodynamic therapy with verteporfin for polypoidal choroidal vasculopathy. *Eye* 2009; 23: 1417–1422.
 108. Lee SC, Seong YS, Kim SS, *et al.* Photodynamic therapy with verteporfin for polypoidal choroidal vasculopathy of the macula. *Ophthalmologica* 2004; 218: 193–201.
 109. Kurashige Y, Otani A, Sasahara M, *et al.* Two-year results of photodynamic therapy for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2008; 146: 513–519.
 110. Akaza E, Yuzawa M and Mori R. Three-year follow-up results of photodynamic therapy for polypoidal choroidal vasculopathy. *Jpn J Ophthalmol* 2011; 55: 39–44.

111. Hirami Y, Tsujikawa A, Otani A, *et al.* Hemorrhagic complications after photodynamic therapy for polypoidal choroidal vasculopathy. *Retina* 2007; 27: 335–341.
112. Oishi A, Kojima H, Mandai M, *et al.* Comparison of the effect of ranibizumab and verteporfin for polypoidal choroidal vasculopathy: 12-month LAPTOP study results. *Am J Ophthalmol* 2013; 156: 644–651.
113. Ojima Y, Tsujikawa A, Otani A, *et al.* Recurrent bleeding after photodynamic therapy in polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2006; 141: 958–960.
114. Lee WK, Kim KS, Kim W, *et al.* Responses to photodynamic therapy in patients with polypoidal choroidal vasculopathy consisting of polyps resembling grape clusters. *Am J Ophthalmol* 2012; 154: 355.e1–365.e1.
115. Yamashita A, Shiraga F, Shiragami C, *et al.* One-year results of reduced-fluence photodynamic therapy for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2010; 149: 465.e1–471.e1.
116. Sen P, Bhende M, Sachidanandam R, *et al.* Reduced-fluence photodynamic therapy and anti-vascular endothelial growth factor for polypoidal choroidal vasculopathy in an Indian population. *Indian J Ophthalmol* 2016; 64: 908–913.
117. Ricci F, Calabrese A, Regine F, *et al.* Combined reduced fluence photodynamic therapy and intravitreal ranibizumab for polypoidal choroidal vasculopathy. *Retina* 2012; 32: 1280–1288.
118. Wong IY, Shi X, Gangwani R, *et al.* 1-year results of combined half-dose photodynamic therapy and ranibizumab for polypoidal choroidal vasculopathy. *BMC Ophthalmol* 2015; 15: 66.
119. Matsuoka M, Ogata N, Otsuji T, *et al.* Expression of pigment epithelium derived factor and vascular endothelial growth factor in choroidal neovascular membranes and polypoidal choroidal vasculopathy. *Br J Ophthalmol* 2004; 88: 809–815.
120. Kokame GT, Yeung L and Lai JC. Continuous anti-VEGF treatment with ranibizumab for polypoidal choroidal vasculopathy: 6-month results. *Br J Ophthalmol* 2010; 94: 297–301.
121. Lai TYY, Chan W-M, Liu DTL, *et al.* Intravitreal bevacizumab (Avastin) with or without photodynamic therapy for the treatment of polypoidal choroidal vasculopathy. *Br J Ophthalmol* 2008; 92: 661–666.
122. Hikichi T, Higuchi M, Matsushita T, *et al.* Results of 2 years of treatment with as-needed ranibizumab reinjection for polypoidal choroidal vasculopathy. *Br J Ophthalmol* 2013; 97: 617–621.
123. Marcus DM, Singh H, Lott MN, *et al.* Intravitreal ranibizumab for polypoidal choroidal vasculopathy in non-Asian patients. *Retina* 2013; 33: 35–47.
124. Chhablani JK, Narula R and Narayanan R. Intravitreal bevacizumab monotherapy for treatment-naïve polypoidal choroidal vasculopathy. *Indian J Ophthalmol* 2013; 61: 136–138.
125. Wakabayashi T, Gomi F, Sawa M, *et al.* Intravitreal bevacizumab for exudative branching vascular networks in polypoidal choroidal vasculopathy. *Br J Ophthalmol* 2012; 96: 394–399.
126. Hosokawa M, Shiraga F, Yamashita A, *et al.* Six-month results of intravitreal aflibercept injections for patients with polypoidal choroidal vasculopathy. *Br J Ophthalmol* 2015; 99: 1087–1091.
127. Yamamoto A, Okada AA, Kano M, *et al.* One-year results of intravitreal aflibercept for polypoidal choroidal vasculopathy. *Ophthalmology* 2015; 122: 1866–1872.
128. Hara C, Sawa M, Sayanagi K, *et al.* One-year results of intravitreal aflibercept for polypoidal choroidal vasculopathy. *Retina* 2016; 36: 37–45.
129. Kokame GT, Lai JC, Wee R, *et al.* Prospective clinical trial of intravitreal aflibercept treatment for polypoidal choroidal vasculopathy with hemorrhage or exudation (EPIC study): 6 month results. *BMC Ophthalmol* 2016; 16: 127.
130. Qu J, Cheng Y, Li X, *et al.* Efficacy of intravitreal injection of conbercept in polypoidal choroidal vasculopathy: subgroup analysis of the Aurora study. *Retina* 2016; 36: 926–937.
131. Stangos AN, Gandhi JS, Nair-Sahni J, *et al.* Polypoidal choroidal vasculopathy masquerading as neovascular age-related macular degeneration refractory to ranibizumab. *Am J Ophthalmol* 2010; 150: 666–673.
132. Cho HJ, Kim JW, Lee DW, *et al.* Intravitreal bevacizumab and ranibizumab injections for patients with polypoidal choroidal vasculopathy. *Eye* 2012; 26: 426–433.
133. Yamashita M, Nishi T, Hasegawa T, *et al.* Response of serous retinal pigment epithelial detachments to intravitreal aflibercept in

- polypoidal choroidal vasculopathy refractory to ranibizumab. *Clin Ophthalmol* 2014; 8: 343–346.
134. Miura M, Iwasaki T and Goto H. Intravitreal aflibercept for polypoidal choroidal vasculopathy after developing ranibizumab tachyphylaxis. *Clin Ophthalmol* 2013; 7: 1591–1595.
 135. Gomi F, Sawa M, Wakabayashi T, *et al.* Efficacy of intravitreal bevacizumab combined with photodynamic therapy for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2010; 150: 48.e1–54.e1.
 136. Ruamviboonsuk P, Tadarati M, Vanichvaranont S, *et al.* Photodynamic therapy combined with ranibizumab for polypoidal choroidal vasculopathy: results of a 1-year preliminary study. *Br J Ophthalmol* 2010; 94: 1045–1051.
 137. Saito M, Iida T, Kano M, *et al.* Two-year results of combined intravitreal ranibizumab and photodynamic therapy for polypoidal choroidal vasculopathy. *Graefes Arch Clin Exp Ophthalmol* 2013; 251: 2099–2110.
 138. Lee YH, Lee E-K, Shin KS, *et al.* Intravitreal ranibizumab combined with verteporfin photodynamic therapy for treating polypoidal choroidal vasculopathy. *Retina* 2011; 31: 1287–1293.
 139. Koh A, Lai TYY, Takahashi K, *et al.* Efficacy and safety of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: a randomized clinical trial. *JAMA Ophthalmol* 2017; 135: 1206–1213.
 140. Lee WK, Iida T, Ogura Y, *et al.* Efficacy and safety of intravitreal aflibercept for polypoidal choroidal vasculopathy in the PLANET study: a randomized clinical trial. *JAMA Ophthalmol* 2018; 136: 786–793.
 141. Lee Y-A, Yang C-H, Yang C-M, *et al.* Photodynamic therapy with or without intravitreal bevacizumab for polypoidal choroidal vasculopathy: two years of follow-up. *Am J Ophthalmol* 2012; 154: 872.e2–880.e2.
 142. Kim M, Kim K, Kim DG, *et al.* Two-year results of photodynamic therapy combined with intravitreal anti-vascular endothelial growth factor for polypoidal choroidal vasculopathy. *Ophthalmologica* 2011; 226: 205–213.
 143. Nemoto R, Miura M, Iwasaki T, *et al.* Two-year follow-up of ranibizumab combined with photodynamic therapy for polypoidal choroidal vasculopathy. *Clin Ophthalmol* 2012; 6: 1633–1638.
 144. Tomita K, Tsujikawa A, Yamashiro K, *et al.* Treatment of polypoidal choroidal vasculopathy with photodynamic therapy combined with intravitreal injections of ranibizumab. *Am J Ophthalmol* 2012; 153: 68.e1–80.e1.
 145. Wakabayashi T, Gomi F, Sawa M, *et al.* Marked vascular changes of polypoidal choroidal vasculopathy after photodynamic therapy. *Br J Ophthalmol* 2008; 92: 936–940.
 146. Sagong M, Lim S and Chang W. Reduced-fluence photodynamic therapy combined with intravitreal bevacizumab for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2012; 153: 873.e2–882.e2.
 147. Yoshida Y, Kohno T, Yamamoto M, *et al.* Two-year results of reduced-fluence photodynamic therapy combined with intravitreal ranibizumab for typical age-related macular degeneration and polypoidal choroidal vasculopathy. *Jpn J Ophthalmol* 2013; 57: 283–293.
 148. Oishi A, Miyamoto N, Mandai M, *et al.* LAPTOP study: a 24-month trial of verteporfin versus ranibizumab for polypoidal choroidal vasculopathy. *Ophthalmology* 2014; 121: 1151–1152.
 149. Lee M-W, Yeo I, Wong D, *et al.* Argon laser photocoagulation for the treatment of polypoidal choroidal vasculopathy. *Eye* 2009; 23: 145–148.
 150. Yuzawa M, Mori R and Haruyama M. A study of laser photocoagulation for polypoidal choroidal vasculopathy. *Jpn J Ophthalmol* 2003; 47: 379–384.
 151. Lai TYY, Chan W-M and Lam DSC. Laser photocoagulation of indocyanine green angiographically identified feeder vessels to idiopathic polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2004; 138: author reply 694: 693–694; author reply 694.
 152. Okubo A, Ito M, Kamisasanuki T, *et al.* Visual improvement following trans-Tenon's retrobulbar triamcinolone acetonide infusion for polypoidal choroidal vasculopathy. *Graefes Arch Clin Exp Ophthalmol* 2005; 243: 837–839.
 153. Mukai R, Kishi S, Sato T, *et al.* Protective effect of intravitreal bevacizumab and sub-tenon triamcinolone acetonide against occlusion of choriocapillaris induced by photodynamic therapy. *Ophthalmologica* 2010; 224: 267–273.
 154. Nakata I, Tsujikawa A, Yamashiro K, *et al.* Two-year outcome of photodynamic therapy combined with intravitreal injection of bevacizumab and triamcinolone acetonide for

- polypoidal choroidal vasculopathy. *Graefes Arch Clin Exp Ophthalmol* 2013; 251: 1073–1080.
155. Lai TYY, Lam CPS, Luk FOJ, *et al.* Photodynamic therapy with or without intravitreal triamcinolone acetonide for symptomatic polypoidal choroidal vasculopathy. *J Ocul Pharmacol Ther* 2010; 26: 91–95.
156. Chan W-M, Liu DTL, Lai TYY, *et al.* Extensive submacular haemorrhage in polypoidal choroidal vasculopathy managed by sequential gas displacement and photodynamic therapy: a pilot study of one-year follow up. *Clin Exp Ophthalmol* 2005; 33: 611–618.
157. Chen CY, Hooper C, Chiu D, *et al.* Management of submacular hemorrhage with intravitreal injection of tissue plasminogen activator and expansile gas. *Retina* 2007; 27: 321–328.
158. Nayak S, Padhi TR, Basu S, *et al.* Pneumatic displacement and intra-vitreous bevacizumab in management of sub-retinal and sub-retinal pigment epithelial hemorrhage at macula in polypoidal choroidal vasculopathy (PCV): rationale and outcome. *Semin Ophthalmol* 2015; 30: 53–55.
159. Wu T-T, Kung Y-H and Hong M-C. Vitreous hemorrhage complicating intravitreal tissue plasminogen activator and pneumatic displacement of submacular hemorrhage. *Retina* 2011; 31: 2071–2077.
160. Shiraga F, Matsuo T, Yokoe S, *et al.* Surgical treatment of submacular hemorrhage associated with idiopathic polypoidal choroidal vasculopathy. *Am J Ophthalmol* 1999; 128: 147–154.
161. Schweitzer C, Bonnel S, Le Mer Y, *et al.* Surgical management of sub-retinal haemorrhage secondary to polypoidal choroidal vasculopathy. *J Fr Ophthalmol* 2011; 34: 557.e1–577.e1.
162. Lin T-C, Hwang D-K, Lee F-L, *et al.* Visual prognosis of massive submacular hemorrhage in polypoidal choroidal vasculopathy with or without combination treatment. *J Chin Med Assoc* 2016; 79: 159–165.
163. Hauptert CL, McCuen BW 2nd, Jaffe GJ, *et al.* Pars plana vitrectomy, subretinal injection of tissue plasminogen activator, and fluid-gas exchange for displacement of thick submacular hemorrhage in age-related macular degeneration. *Am J Ophthalmol* 2001; 131: 208–215.
164. Martel JN and Mahmoud TH. Subretinal pneumatic displacement of subretinal hemorrhage. *JAMA Ophthalmol* 2013; 131: 1632–1635.