

Polypoidal Choroidal Vasculopathy: An Update on Therapeutic Approaches

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Polypoidal choroidal vasculopathy (PCV) is a retinal disease involving the choroidal vasculature characterized by the presence of polypoidal lesions with or without branching vascular network best seen on indocyanine green angiography (ICGA). Clinical features of PCV include recurrent subretinal hemorrhage; serosanguineous pigment epithelial detachment, subretinal exudation and serous retinal detachment. PCV is more prevalent among Asians and Blacks as compared to Caucasians and has been found to account for 25 to 50% of cases of presumed neovascular age-related macular degeneration in Asian patients. Treatment is indicated in patients with symptomatic PCV due to potentially irreversible visual loss. Various treatment modalities for symptomatic PCV have been described in the literature, including thermal laser photocoagulation, ICGA-guided photodynamic therapy (PDT) with verteporfin, anti-vascular endothelial growth factor (VEGF) therapy, and combined PDT and anti-VEGF therapy. This review aims to provide an update on the therapeutic options for PCV, with particular reference to recent studies published in the past two years.

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INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) is a retinal disorder characterized by the presence of aneurysmal polypoidal lesions in the choroidal vasculature. It has been considered to be a variant of neovascular age-related macular degeneration (AMD).¹⁻³ The aneurysmal dilatations, also known as polyps, may be found at subfoveal, juxtafoveal, extrafoveal, peripapillary or even peripheral regions. These polypoidal dilatations may be visible as reddish-orange subretinal nodules during ophthalmoscopic examination. The polypoidal lesions are best detected on

indocyanine green angiography (ICGA) and might be associated with a branching vascular network (BVN) of neovascularization.^{3,4} The presence of choroidal polyps and BVN can lead to recurrent episodes of exudative retinal detachment, serous or hemorrhagic pigment epithelial detachment (PED), subretinal hemorrhage, and subretinal exudation.¹⁻³ Several reviews have been published in recent years on the diagnosis and treatment of PCV. The main purpose of the current review is to provide an update on the therapeutic options for PCV with particular reference to studies published in the past two years.

Epidemiology of PCV

PCV predominantly occurs in middle-aged to elderly subjects and most commonly affects patients in their 50s or 60s.⁵ It can affect both genders, although more often in men than women and in Asian populations.^{6,7} The prevalence of PCV varies among different ethnic groups and has a higher prevalence in Asians and Blacks as compared to Caucasians.² PCV accounts for 25-50% of Asian patients presenting with presumed neovascular AMD,⁷⁻¹⁰ whereas it is seen in only 5-10% of Caucasian patients with neovascular AMD.¹¹⁻¹³

Recent epidemiological studies conducted in Asian populations have confirmed most of the findings published in previous reports.⁶⁻¹⁰ A study on 204 Chinese patients with PCV reported mean age at presentation to be 66.1 years with 60.3% male subjects; 79.4% of these cases were unilateral.¹⁴ Chang et al, reported that among 100 patients with presumed neovascular AMD, 49% were found to be PCV on ICGA examination.¹⁵ Mean age of these patients was 63.6 years with male predominance of 71.4%; 91.8% of the patients had unilateral disease.¹⁵ A Korean epidemiology study, on the other hand, showed only 22.2% of their presumed neovascular AMD patients to be suffering from PCV.¹⁶

Smoking is a known risk factor for AMD and also appears to be an important risk factor for PCV. A Japanese study demonstrated that cigarette smoking is associated with an odds ratio of 4.87 for PCV when compared with normal controls.¹⁷ This finding was supported by Cackett et al, who reported an odds ratio of 4.4 for smokers.¹⁸ For patients with unilateral PCV, the presence of late geographic hyperfluorescence, a well-demarcated geographic hyperfluorescent lesion on late phase ICG angiograms, has been found to be a significant risk factor for the development of PCV in the fellow eye.¹⁹

Studies have been conducted to evaluate genetic variants that might be associated with PCV. A GG missense variant at rs5882 in the cholesteryl ester transfer protein (CETP) locus was found to have a 3.53-fold increased risk of PCV compared with the AA genotype.²⁰ In

addition to the increased risk of PCV, patients with the rs5882 GG genotype were also noted to have lower serum high-density lipoprotein levels than the AA genotype.²⁰ The major genetic risk factors for neovascular AMD, complement factor H gene (*CFH*) Y402H and *ARMS2* A69S polymorphisms were also found to be associated with increased risk of having PCV as compared to controls, with odds ratios of 1.63 and 2.26, respectively.²¹ The *CFH* Y402H polymorphism might also have a synergistic effect with cigarette smoking to further increase the risk of PCV.²¹

For patients already diagnosed with PCV, a single nucleotide polymorphism at rs10490924 in *ARMS2* was found to be significantly associated with visual prognosis following verteporfin photodynamic therapy (PDT).^{22,23} In particular, the GG genotype at rs10490924 was found to have better visual outcome post-PDT when compared with the TT genotype.^{22,23} Another study revealed that the AA genotype at rs12603825 in the *SERPINF1* gene is associated with significantly shorter re-treatment free periods after PDT than other genotypes.²⁴

Investigations for PCV

Since fluorescein angiography (FA) findings of PCV can mimic those of occult choroidal neovascularization (CNV) in neovascular AMD (Fig. 1A), visualization of the abnormal polypoidal lesions with ICGA is required to differentiate PCV from CNV in neovascular AMD.^{25,26} ICGA can demonstrate single or multiple polyps as vascular aneurysmal dilatations arising from inner choroidal vessels in the early phase as hyperfluorescent spots with subsequent late hypofluorescence surrounded by ring-like silhouette staining of polyps (Fig. 1B&C).^{4,6} Occasionally, a BVN might also be seen on ICGA. A recently published guideline on the diagnosis and treatment of PCV has defined PCV as "the presence of single or multiple focal areas of hyperfluorescence arising from the choroidal circulation within the first 6 minutes after injection of ICG, with or without an associated BVN. The presence of orange-red subretinal nodules with corresponding ICG hyperfluorescence is pathognomonic of

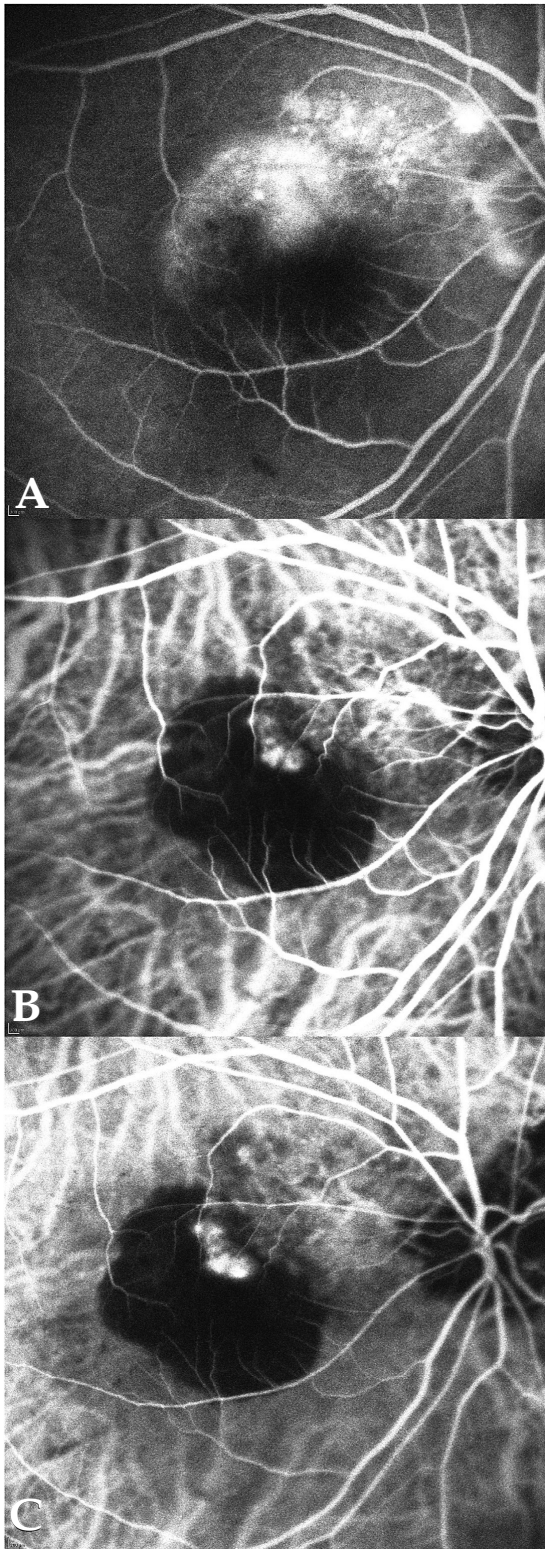


Figure 1. (A) Late phase fluorescein angiography of polypoidal choroidal vasculopathy appearing as occult choroidal neovascularization. (B) Early and (C) mid-phase indocyanine green angiography shows polypoidal lesions with branching vascular network and pigment epithelial detachment.

PCV.²⁷ Optical coherence tomography (OCT) imaging, though not essential for the diagnosis of PCV, may help visualize the polypoidal lesion as a dome-shaped anterior elevation of highly reflective retinal pigment epithelial (RPE) layers with regions of low to moderate reflectivity beneath the RPE line.²⁷ OCT may also help in the detection of subretinal fluid and PED which can reflect the PCV and will be useful in monitoring the response to treatment.

Natural Course of PCV

Patients with PCV can be asymptomatic if there is no leakage from the polypoidal lesions. Patients with symptomatic PCV can present both acutely or with progressive visual loss. Acute visual loss in PCV is usually secondary to spontaneous rupture of the polypoidal lesions, which in turn leads to submacular hemorrhage causing scotoma or even breakthrough vitreous hemorrhage with severe visual loss. Patients may also present with progressive visual loss with metamorphopsia due to accumulation of subretinal fluid and exudates around the polypoidal lesion. The natural course of PCV is variable and it has been estimated that 50% of patients will have a favorable course, in which spontaneous regression of polyps can occur without treatment.²⁸ However, in the remaining half, repeat bleeding and leakage will result in RPE and photoreceptor degeneration, scarring and irreversible visual loss. It has been suggested that the presence of a grape-like cluster of polyps might be a risk factor for poor visual prognosis due to higher risk of bleeding.^{28,29} In a retrospective study by Kwok et al, it was found that after a mean follow-up of 28.2 months without treatment, there was mean loss of 3.1 Snellen lines among PCV patients, with 76.9% of cases having final vision of 20/200 or worse.²⁶ In view of the high proportion of PCV patients with poor visual outcome without treatment, active intervention is indicated in patients with symptomatic PCV.

Photodynamic Therapy for PCV

PDT with verteporfin is one of the most widely described treatment modalities for PCV in

the literature. Before PDT, ICGA should be performed to evaluate the location and size of the PCV lesions. The PDT laser spot size is generally determined by the greatest linear dimension (GLD) of the lesion, including both polyps and interconnecting BVN based on ICGA. Most clinicians use the standard protocol of verteporfin infusion as described by the Treatment of Age-related macular degeneration with Photodynamic therapy (TAP) study group.³⁰⁻³⁵ Verteporfin is infused intravenously at a dose of 6mg/m² of body surface area over 10 minutes, followed by application of 689nm laser 15 minutes after initiation of infusion with a light dose of 50 J/cm² over 83 seconds. Patients should be warned to avoid excessive sunlight exposure for a few days after PDT. Application of the non-thermal PDT laser on the targeted region is thought to induce transient local choroidal vascular occlusion, which reduces perfusion to PCV lesions and subsequently leads to thrombosis of supplying choroidal vessels, and finally results in regression of PCV lesions.³⁶ Younger age, smaller lesion GLD, better baseline vision and less baseline hemorrhage are significant and independent factors predictive of better visual outcomes one year after PDT monotherapy.³⁷ Since PDT might not be completely effective in causing BVN occlusion,³⁸ FA and ICGA should be repeated at 3 months and re-treatment should be considered when FA and ICGA demonstrate persistent or new polyps.

Most studies on PDT monotherapy for PCV have reported favorable short to mid-term results, with stable or improved vision and regression of polyps achieved in 80%-95% of eyes.³¹⁻³⁵ Mori et al, evaluated 181 PCV patients who underwent PDT monotherapy and noticed that by one year, mean Snellen visual acuity improved from 0.29 to 0.43, with 30.4% and 60.8% of patients having improved or stabilized vision respectively.³⁹ Gomi et al, reported that mean visual acuity improved from 49.5 to 56.3 Snellen letters at 1 year in 36 PCV patients treated with PDT, with visual acuity improved in 67% and stabilized in 17% of cases at 12 months.⁴⁰ Although 5.6% of patients had recurrence of PCV, 86% had complete regression of polyps

and cessation of FA leakage by the end of the study.⁴⁰ Otani et al, conducted a retrospective study on 45 PCV eyes that were treated with PDT and were followed for 12 months. Mean logMAR visual acuity improved from 0.58 to 0.46 one year after PDT and 82.2% showed complete regression of polyps.⁴¹ However, it was concluded that despite PDT, there was little regression of the surrounding BVN.⁴¹

Although the short-term visual outcome of PDT monotherapy for PCV appeared promising, a 5-year multi-centered prospective study of 65 PCV patients showed that patients had a mean decline of 0.21 logMAR units in best corrected visual acuity (BCVA) from baseline to 5 years after the initiation of PDT monotherapy.⁴² The study also showed that poorer pre-treatment BCVA, older age and larger lesion dimension are major risk factors for poor visual outcomes at 60 months after PDT. Another 3-year study which evaluated 43 eyes treated with PDT monotherapy also reported that mean BCVA dropped below baseline at 36 months with a recurrence rate of 77% during the study period.⁴³ In contrary, a retrospective study with 5-year follow-up on 42 eyes treated with PDT reported visual improvement in 33.3%, stable vision in 54.8% and visual deterioration in 11.9%.⁴⁴ However, despite the apparently favorable long-term visual outcome, 78.6% of eyes were found to have recurrence of polyps during the five-year follow-up period. In another prospective study in which 27 PCV patients completed 3 years of follow-up, 14.8% of eyes had improved vision and 74.1% had stable vision by the end of the third year.⁴⁵ Despite the fact that 59.3% of eyes developed recurrence of polyps, all of them responded well to re-treatment and did not suffer from additional BCVA loss.⁴⁵ In view of high recurrence rate, long-term follow-up is required for PCV patients who are treated with PDT.⁴⁶

Complications of PDT for PCV include post-PDT hemorrhage, massive supra-choroidal hemorrhage, RPE tears and microrips at the margin of the PED, with post-PDT subretinal hemorrhage being the most common complication.⁴⁷⁻⁴⁹ Hiramani et al, demonstrated that among 91 PCV eyes managed with PDT, 30.8%

developed post-PDT subretinal hemorrhage. However, despite post-PDT subretinal hemorrhage, visual acuity was maintained or increased in 81.8% of these eyes and 78.6% of hemorrhages resolved spontaneously without treatment.⁴⁷ In 21.4% of eyes, the condition was further complicated by vitreous hemorrhage and it was found that larger PDT laser spot size was associated with a higher risk of vitreous hemorrhage.⁴⁷

The standard dose of PDT might be associated with possible adverse effects on the choriocapillaris surrounding the treatment zone due to up-regulation of vascular endothelial growth factor (VEGF).^{50,51} As a result, variations of PDT techniques including half-fluence PDT (300 mW/cm², light dose 25 J/cm²) or even quarter-fluence PDT have been developed.⁵² Yamashita et al, showed that the use of reduced fluence PDT (light dose 25 J/cm²) in 38 PCV patients resulted in significant improvement in mean logMAR BCVA from baseline of 0.43 to 0.28 at 12 months and that mean visual acuity remained at 0.29 logMAR after 24 months.⁵³ Improved or stable vision was achieved in 95% of treated patients at 24 months. Further studies to evaluate the role of reduced fluence PDT in the treatment of PCV are therefore warranted.

Anti-VEGF Therapy for PCV

A previous immunohistological study has demonstrated that specimens of choroidal neovascular membranes collected from PCV eyes showed strong expression of both pigment epithelium derived factor (PEDF) and VEGF in the vascular endothelial cells and RPE cells.⁵⁴ Elevated levels of PEDF and VEGF have also been found in the aqueous humor of PCV patients.⁵⁵ Since PEDF is an inhibitor of ocular angiogenesis and cell proliferation, Matsuoka proposed that the interaction between PEDF and VEGF may modulate the formation of subfoveal fibrovascular membranes.⁵⁴ These findings support the theoretical role of anti-VEGF therapy for management of PCV.

Various studies have found that anti-VEGF therapy may reduce subretinal fluid and cause stabilization of vision in eyes with

PCV.⁵⁶⁻⁵⁸ However, choroidal vascular changes on ICGA generally persisted despite anti-VEGF treatment.⁵⁶ Kokame et al, reported that monthly intravitreal injections of ranibizumab resulted in visual stabilization in all twelve PCV patients at 6 months, with macular edema and subretinal fluid improved in 80% and 63% of eyes respectively.⁵⁷ However, reduction in polyps was only observed in 33% of patients.⁵⁷ Lai et al, also showed that three monthly intravitreal bevacizumab injections in PCV patients had limited effect on regression of polyps, since polyps persisted in all patients at 3 months despite visual improvement and reduction in central foveal thickness.⁵⁸ Hikichi et al, recently reported the results of their two-year prospective study on the use of intravitreal ranibizumab monotherapy in 75 PCV patients.⁵⁹ All patients received three monthly loading doses of intravitreal ranibizumab injections followed by as-needed re-injections. Mean logMAR BCVA improved from 0.59 at baseline to 0.37 and 0.41 logMAR at 12 months and 24 months respectively. Complete regression of polyps was achieved in 40% and 25% of patients at 12 and 24 months, respectively. Despite the promising visual outcome, BVN persisted in all patients and tended to increase in size during the second year.⁵⁹ Similar visual improvement was also noted in non-Asian populations. Marcus et al, reported that among twenty PCV eyes treated with three initial monthly followed by as-needed intravitreal ranibizumab injections, mean BCVA increased from baseline by 1.2 Snellen lines at 12 months and 24 months.⁶⁰ Chhablani et al, followed 9 eyes of 8 PCV patients who underwent intravitreal bevacizumab injections followed by repeat treatment as required for a mean duration of 8.4 months.⁶¹ In this study, subretinal fluid and subretinal hemorrhage resolved in all eyes and seven eyes had improved vision and the two remaining eyes maintained stable vision during the study period. However, persistent polyps were noted in 3 (33.3%) eyes. In a study comparing the effect of intravitreal ranibizumab and bevacizumab in PCV patients, Cho et al, concluded there was no significant difference in terms of visual improvement, reduction in foveal thickness and regression of polyps between the

two anti-VEGF agents at 12 months.⁶² Despite the statistically significant visual improvement and reduction in foveal thickness after anti-VEGF monotherapy, polyps only regressed in 23.3% and 24.2% of eyes in the ranibizumab and bevacizumab treated groups respectively. In view of differences in treatment response to anti-VEGF therapy between PCV and neovascular AMD patients, it is essential to perform ICGA in patients presenting as neovascular AMD but refractory to anti-VEGF therapy to exclude PCV as the underlying cause.²⁶

Combined PDT and anti-VEGF Therapy

Although PDT seems to be effective in improving vision and inducing regression of polyps among PCV patients, it is not ideal in view of the high recurrence rate and the risk of complications such as post-PDT subretinal hemorrhage. The up-regulation of VEGF levels in PCV eyes following PDT may account for the development of secondary CNV and recurrence of PCV. Therefore, adjunctive treatment with intravitreal anti-VEGF therapy at the time of PDT may suppress the pro-angiogenic activity of VEGF. PDT in the form of combined therapy for PCV is targeted to cause thrombosis of the polypoidal lesions and anti-VEGF therapy may tackle the CNV-like BVN to reduce the amount of exudation caused by PCV lesions. Recent studies have also suggested that combined PDT and intravitreal anti-VEGF therapy might result in less post-PDT subretinal hemorrhage than PDT alone.^{63,64}

Various studies have demonstrated that combined PDT and anti-VEGF treatment is more effective than anti-VEGF monotherapy in causing regression of polypoidal lesions on ICGA.^{58,65,66} Gomi et al reported that despite similar polyp resolution and recurrence rates among PCV eyes treated with combined PDT and intravitreal bevacizumab compared with PDT monotherapy, patients in the combined therapy group had significantly better visual outcome than the monotherapy group at 3, 6, 9 and 12 months.⁶⁷ Moreover, the risk of developing early post-PDT subretinal hemorrhage was shown to be significantly lower in the combined therapy

group (4.7% vs. 17.7%).⁶⁷ Ruamviboonsuk et al, also reported promising results with combined PDT and intravitreal ranibizumab therapy, in which mean BCVA improved from baseline by 12.3 letters.⁶⁶ BCVA improvement of 15 letters or more was observed in 58.3% of patients. Although 8.3% of the patients had loss of BCVA of 15 letters or more, all patients enjoyed complete regression of polyps without recurrence at 12 months. The beneficial effects of combined PDT and anti-VEGF therapy have been confirmed by the EVEREST study, a phase 3, double-blind, multi-center, randomized controlled trial, which evaluated the efficacy of intravitreal ranibizumab monotherapy versus verteporfin PDT monotherapy versus combined therapy with PDT and intravitreal ranibizumab for treatment of PCV.⁶⁸ The study showed that both combination therapy and PDT monotherapy resulted in a significantly higher proportion of PCV eyes having complete regression of polyps on ICGA than ranibizumab alone at 6 months (77.8% vs. 71.4% vs. 28.6% respectively).⁶⁸

Several recent reports have described the longer-term efficacy of combined PDT and intravitreal anti-VEGF therapy. A retrospective study by Saito et al compared PDT monotherapy in 32 PCV patients with 25 PCV patients treated with PDT plus intravitreal ranibizumab and all patients were followed for at least 24 months.⁶⁵ Patients who received combined PDT and intravitreal ranibizumab were found to have better vision gain as compared to the control group using PDT alone. Mean BCVA change in the combined treatment group was +2.63 versus -0.16 lines in the PDT monotherapy group at 24 months. Moreover, none of the patients in the combined therapy group developed new subretinal hemorrhage, as compared to eight (25%) patients in the PDT monotherapy group. A similar conclusion was drawn in a study by Lee et al, which evaluated 17 PCV patients treated with combined PDT and intravitreal ranibizumab.⁶⁹ Mean logMAR BCVA improved from 0.43 at baseline to 0.11 at 12 months and mean central foveal thickness also decreased from 351 microns at baseline to 204 microns at 12 months. Besides intravitreal ranibizumab, Kim et al, also

evaluated the effect of combination therapy with PDT and intravitreal bevacizumab.⁷⁰ At 12 months, mean BCVA gain from baseline was 3.0 lines in the combined therapy group but only 1.6 lines in the PDT monotherapy group.

Despite these encouraging results, a 2-year prospective study on 22 PCV patients treated with combined PDT and intravitreal ranibizumab therapy revealed less optimal visual outcomes.⁷¹ Although mean central retinal thickness of PCV patients was significantly reduced from baseline during the entire follow-up period, the initial visual gain started to diminish after 9 months and final visual improvement at 24 months was only 2.9 letters.⁷¹ These findings were supported by another retrospective study on 22 PCV patients who received PDT followed by intravitreal bevacizumab or ranibizumab within 7 days.⁷² Although mean logMAR BCVA improved from 0.43 at baseline to 0.28 at 12 months, mean logMAR BCVA dropped back to 0.39 at 24 months.⁷² Thus, a decline in the initial beneficial effects of combined therapy might be observed over time. Lee et al, also concluded that although combined PDT and intravitreal bevacizumab therapy appeared to result in more visual gain than PDT monotherapy, this effect was only observed in the first 6 months.⁷³ The efficacy between the two treatment modalities was not statistically different for visits from 6 months to 2 years.⁷³ However, one should note the methodology adopted by Lee et al, as they applied PDT one week after intravitreal injection of bevacizumab rather than before anti-VEGF injections as in most other studies. Since the intravitreal half-life of bevacizumab in the eye is around 4.3 days,⁷⁴ the synergetic effect of combined therapy might be reduced with delayed PDT application.

Although combination treatment with PDT and intravitreal anti-VEGF appeared to be beneficial for PCV patients in the initial 6-12 months, Tomita et al, reported among 27 patients who had received PDT monotherapy prior to combination treatment, mean logMAR BCVA deteriorated from 0.61 to 0.68 at 12 months.⁷⁵ Therefore, combined therapy was unable to result in significant visual gain in patients already treated with PDT.

Combination therapy with reduced fluence PDT (RF-PDT) and intravitreal bevacizumab might be an alternative to the usual combination therapy with standard fluence PDT and intravitreal anti-VEGF agents.^{76,77} Sagong et al, showed at 12 months, 93.8% of PCV patients treated with combined RF-PDT and intravitreal bevacizumab therapy had improved (56.3%) or stable (37.5%) vision.⁷⁶ Although 18.8% of cases were noted to have recurrence of polyps, none of the subjects developed severe complications such as subretinal hemorrhage, uveitis or endophthalmitis.⁷⁶ Yoshida et al, treated 14 PCV patients with RF-PDT and three monthly injections of intravitreal ranibizumab followed by as required intravitreal ranibizumab retreatments with or without RF-PDT.⁷⁷ Following treatment, BCVA of all patients was maintained at 12 months and at 24 months; 92.9% of these patients maintained their initial BCVA.⁷⁷ In this 2-year study, mean BCVA was shown to increase continuously throughout the 24 month period. Ricci et al, also used RF-PDT by reducing the laser exposure time from 83s to 70s combined with intravitreal ranibizumab at 48 hours to treat 17 patients with PCV.⁷⁸ At 12 months, mean logMAR BCVA improved from 0.45 to 0.29 and 95% of these patients had improved or stable vision during the study period. These small case series suggested combination treatment using RF-PDT and anti-VEGF agents might also be useful for PCV but further controlled studies are required to evaluate the role of standard PDT versus RF-PDT in combination therapy for PCV.

In addition to the use of combination treatment with PDT and anti-VEGF agents, triple therapy using PDT, anti-VEGF agents and intravitreal steroid injection has also been used for treating PCV.⁷⁹ Nakata et al, reviewed 40 consecutive PCV patients of whom 16 were treated with standard PDT monotherapy while others underwent triple therapy with standard fluence PDT, intravitreal bevacizumab and intravitreal triamcinolone.⁷⁹ For patients receiving triple therapy, intravitreal injections were performed 3 days prior to standard fluence PDT. At 24 months, 12.5% of patients in the PDT treated group compared to 41.7% of those in the triple therapy group showed vision

improvement. Triple therapy also appeared to be more effective in reducing retreatment rates and post-treatment vitreous hemorrhage as the re-treatment rate of the triple therapy group was half that of the PDT group (75.0% versus 37.5%), and post-treatment vitreous hemorrhage occurred in 12.5% of the PDT group but none in the triple therapy group.

Intravitreal or Subtenon Triamcinolone Acetonide

The use of trans-tenon retrobulbar injections of 12mg triamcinolone acetonide (TA) has been reported in a patient with PCV.⁸⁰ Following treatment, the size of the polyp was reduced and subretinal fluid resolved completely. On the other hand subtenon triamcinolone has been suggested to reduce the occlusive effect of PDT on the choriocapillaris at the marginal zone of the treated area.⁸¹ Lai et al demonstrated that mean visual acuity at 2 years in PCV eyes treated with PDT and intravitreal TA did not differ significantly from the PDT monotherapy group. Side effects such as increased risk of cataract formation and ocular hypertension were more frequent in the combined therapy group.⁸² In view of the unclear benefits of TA for management of PCV and the increased risk of steroid-related complications following periocular or intravitreal TA injections, TA should not be used as a routine treatment for PCV unless further studies demonstrate beneficial effects.

Direct Thermal Laser Photocoagulation

Direct thermal laser photocoagulation with argon green, double-frequency Nd:YAG or diode lasers may be utilized for treatment of PCV with extrafoveal polyps by applying the laser to the polyps and to the surrounding BVN based on ICGA.³⁶ Lafaut et al, reported that direct thermal laser photocoagulation achieved regression of polyps in all five patients with peripapillary polyps but only five (55.5%) out of nine patients with macular polyps.¹¹ A retrospective study by Lee et al, showed that 64.3% of PCV eyes treated with direct thermal laser had clinical or angiographic resolution of

maculopathy.⁸³ Furthermore, 78% of eyes with extrafoveal PCV had improved or stable vision one year after laser treatment. However, 10.7% of these laser treated eyes were noted to have subfoveal recurrence of polyps and another 10.7% were found to have secondary CNV formation.⁸³ Yuzawa et al, demonstrated 90% of eyes in which laser was applied to both the polyps and abnormal vessels showed resolution of exudation or blood with improved or stable vision.⁸⁴ However, for eyes in which laser was applied only to the polypoidal lesions but not the surrounding abnormal vessels, 54% showed reduced vision due to recurrent or persistent exudation, development of secondary CNV, or foveal atrophy induced by the thermal laser.

Potential complications of thermal laser photocoagulation include formation of chorioretinal scars, secondary CNV, RPE tears, subretinal or sub-RPE hemorrhage and vitreous hemorrhage. Since these complications might have detrimental effects on vision, direct laser therapy should only be considered in symptomatic PCV patients where polyps and BVN are located far away from the fovea. Moreover, if PCVs are to be managed with laser photocoagulation, the whole lesion including both the polyps and the BVN should be treated.⁸⁴

Pneumatic Displacement

PCV patients may present with massive submacular hemorrhage (>4 disc areas) as a consequence of rupture of polypoidal lesions. Thick subretinal hemorrhage will prevent light transmission to and from layers beneath the subretinal blood, causing difficulty in interpretation of FA and ICGA. In these cases, if the patient presents within 10 to 14 days of the onset of subretinal hemorrhage, pneumatic displacement of the hemorrhage can be considered.³⁶ The procedure of pneumatic displacement involves intravitreal injection of 0.3-0.4mL of 100% perfluoropropane (C3F8) through the pars plana, followed by prone positioning. Perfusion of the optic nerve is checked immediately after the injection of gas and if raised intraocular pressure is noted, anterior chamber paracentesis should be

performed.³⁶ The subretinal hemorrhage will usually be displaced from the macula 1-2 weeks after the procedure. Subsequent FA and ICGA can then be performed to evaluate the previously blocked macular regions. If an active polypoidal lesion is noted on FA and ICGA, PDT with or without intravitreal anti-VEGF injection can be considered. On the other hand, if the polypoidal lesion has already thrombosed without any active leakage after its spontaneous rupture, intervention might not be necessary. Follow up for resolution of the subretinal hemorrhage and possible recurrences should be continued.

Chan et al, evaluated the efficacy of sequential gas displacement followed by PDT in PCV patients with thick submacular hemorrhage.⁸⁵ At one year, mean Snellen BCVA improved from 20/307 to 20/57 and none of the patients developed serious complications from treatment. It should be noted that PCV patients have a higher risk of developing vitreous hemorrhage after pneumatic displacement and intravitreal injection of tissue plasminogen activator.⁸⁶ Larger

size of the pre-treatment subretinal hemorrhage was found to be a risk factor for developing subsequent vitreous hemorrhage.

In conclusion, PCV is a common retinal condition in Asian countries and affects 25-50% of Asian patients with presumed neovascular AMD. ICGA is essential in the diagnosis of PCV and should be performed in cases suspected of PCV or in cases of neovascular AMD refractory to anti-VEGF therapy since the choice of treatment and visual prognosis is different for the two conditions. If the symptomatic polyps and BVN are located at a safe distance away from the fovea, direct thermal laser photocoagulation can be considered. For symptomatic polyps with juxtafoveal or subfoveal involvement, verteporfin PDT with or without intravitreal injection of an anti-VEGF agent should be considered (Fig. 2A & 2B). Following treatment, patients should be monitored regularly with OCT, FA and ICGA in order to assess the activity of the polypoidal lesions and to determine the need for re-treatment (Fig. 2C & 2D). In cases

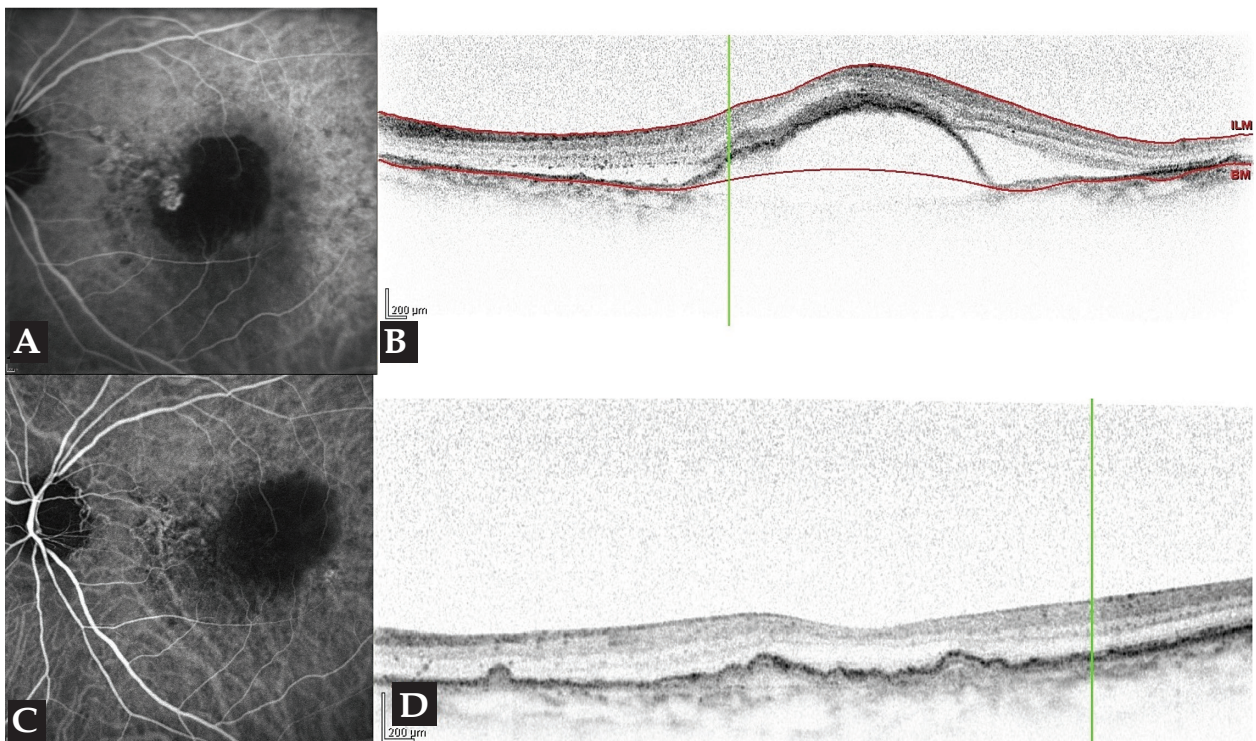


Figure 2. (A) Early phase indocyanine green angiography (ICGA) in polypoidal choroidal vasculopathy shows an active polypoidal lesion with pigment epithelial detachment (PED). (B) Spectral domain optical coherence tomography (SD-OCT) shows PED with adjacent subretinal fluid. (C) Early phase ICGA 3 months after photodynamic therapy and three monthly intravitreal anti-vascular endothelial growth factor injections shows complete regression of polyps and reduced PED. (D) SD-OCT showed resolution of PED and subretinal fluid after treatment.

with symptomatic exudative changes alone without evidence of active polypoidal lesion on angiography, anti-VEGF monotherapy might be considered. For PCV with subretinal hemorrhage larger than 4 disc areas presenting within 10-14 days of onset, pneumatic displacement of the subretinal hemorrhage can be performed for subsequent investigations with angiography. Verteporfin PDT with or without anti-VEGF therapy can then be performed in cases with visible polyps after gas displacement. Finally, all PCV patients who have received treatment should be monitored regularly in the long-term due to the high risk of PCV recurrence.

Conflicts of Interest

None.

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