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Polypoidal Choroidal Vasculopathy

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Abstract

Purpose of review: The aim of this review is to summarize developments in the treatment of active polypoidal choroidal vasculopathy (PCV). PCV is associated with a poor visual prognosis as a consequence the condition's hallmark polypoidal dilatation and a branching network resulting in recurrent hemorrhages and serous leakage.

Recent findings: Recent research has provided new insights into the pathogenesis of PCV. While still considered a subtype of age-related macular degeneration, suggestions that PCV belongs to a spectrum of conditions that present with a pachychoroid are increasingly well accepted. Treatment remains challenging. Combination therapy (photodynamic therapy (PDT) and intravitreal anti-vascular endothelial growth factor (VEGF)) is associated with higher polyp closure rate, but polyp closure rate has not been correlated with superior visual outcomes. Current data points to non-inferiority of anti-VEGF alone versus combined with PDT when final vision acuity is the study outcome.

Summary: PCV remains a clinical challenge. Classification and treatment of the condition continues to evolve. Combination therapy may not be superior to anti-VEGF treatment alone in terms of visual acuity outcome, however data on long-term recurrence should be compared in formulating preferred treatment plans.

Keywords

polypoidal choroidal vasculopathy; branching vascular network; serosanguinous retinal pigment epithelium detachment; retinal detachment; vitreous hemorrhage

INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) was first characterized in middle-aged black women presenting with recurrent hemorrhages in the sub-retinal and sub-pigment

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Conflict of Interest

Raquel Goldhardt and Bradley Simon Rosen declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

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epithelium. Clinically PCV is identified by the associated polypoidal dilatation and a branching network within the choroidal circulation resulting in recurrent hemorrhages and serous leakage. PCV has previously been known as peripheral exudative hemorrhagic chorioretinopathy, multiple recurrent serosanguinous retinal pigment epithelial detachments, posterior uveal bleeding syndrome, idiopathic polypoidal vasculopathy.(1) An exudative pattern with predominantly intraretinal hard exudates deposits has been distinguished from a hemorrhagic pattern that can mimic exudative age-related macular degeneration (AMD).(2) More recently PCV has been considered an AMD variant, although drusen, pigmentary changes and atrophy are uncommon. Previous studies imaging and histological studies have demonstrated that the neovascular complexes in PCV lay between the RPE and Bruch's membrane supporting the theory that PCV is not a primary choroidopathy, but a variant of type 1 neovascularization.(3) OCT findings suggest that PCV belongs to a spectrum of conditions where disturbed choroidal circulation manifests as a pachychoroid. The chronicity of PCV vessels and the findings of increased choroidal thickness and permeability in PCV suggest links between chronic central serous chorioretinopathy (CSCR) and PCV.(4) Interestingly, in a series of 27 eyes with chronic CSCR and type 1 neovascularization, 36 percent of patients went on to develop PCV.(5) Furthermore, while studying the increased choroidal permeability in PCV, researcher in Japan, reported increased frequency of multifocal choroidal hyperfluorescence on ICGA in patients with PCV compared to those with AMD.

The natural history of PCV is less well studied than AMD, and has a variable course among different populations. When the polypoidal lesions are visible, they appear orange-red nodules(6), often associated with serosanguinous pigment epithelium detachment (PED). Typically, these lesions are not associated with drusen. When a large PED is present, a notch in its margin frequently indicates the site of polypoidal lesions.

It is important to distinguish PCV and exudative AMD since treatment algorithms and outcome varies. The current gold standard imaging modality for diagnosis of PCV is indocyanine green angiography (ICGA) and is ideally performed when PCV is suspected(7, 8). Race, lesion location, and suboptimal response to anti-VEGF therapy can help point to a correct diagnosis. Additionally, the inability to localize a vascular pigment epithelium detachment or a choroidal neovascular membrane on OCT suggests consideration of PCV.

Poor outcomes have been linked to recurrent bleeding and persistent leakage as well as the formation of grape-like polypoidal choroidal neovascular membranes.(9) More than half of serosanguinous maculopathy in exudative AMD patients result from PCV type lesions. (10) A predictor of favorable outcome is good visual acuity at presentation and extra-macular location of exudate and lesion but even with available treatment options, eyes with PCV have an unpredictable course. Systemic hypertension, elevated C-reactive protein, hyperhomocysteinuria and smoking are systemic risk factors associated with PCV(11–13). Central serous chorioretinopathy is also associated with development of PCV(14–16). The prevalence of reticular pseudodrusen was reported 3.4% in newly diagnosed cases of PCV. (17)

EPIDEMIOLOGY

PCV is thought to have predilection for pigmented individuals(2) with higher prevalence in blacks and Asians (22–62%)(18–20) and men. (20, 21). Nonetheless PCV affects a wide range of ages and races, and both sexes. In the Asian population, males are more affected (63–88%), lesions tend to affect macula and 72–91% are unilateral(21), in contrast with the Caucasian population where PCV is more common in females and with more bilateral presentation (21–55%)(21). PCV manifestations seems to occur earlier if compared to exudative macular degeneration and presents as unilateral disease.

RISK FACTORS

Exudative AMD and PCV share similar risks factors. Smoking, male gender, a higher body mass index, hyperlipidemia and hypertension are risk factors.(11, 22, 23) Since the pathogenesis of PCV remains unsettled, a potential inflammatory role steered by both environmental and genetic factors seems to play a significant role in this process.(21) Serum level of inflammatory markers like C reactive protein also has been associated with PCV. (24) Another inflammatory biomarker, presumably independent of VEGF is IL-23.(25) Genetically polymorphism of the complement factor H (CFH) Y402H, and ARMS2 A69S (26) have been linked to PCV however these associations were not found to be consistent across studies. The CFH mutations was found to be associated with thicker choroid in patients with PCV(27), whereas ARMS2 and HTRA1 mutations with worse disease and outcomes.(28, 29)

IMAGING MODALITIES

ICGA

ICGA is not routinely ordered at the initial visits in patients with serosanguinous maculopathy. This contributes to the under diagnosis of PCV. ICGA sheds light on the abnormal branching vascular network (BVN) and the nodular hyper fluorescence corresponding to polypoidal dilations. In addition, indocyanine green emits near-infrared light, which penetrates the RPE more readily than the green light emitted by fluorescein. (Figure 1A) Diagnosis of PCV requires the presence of focal hyper fluorescence associated with at least one of the following: BVN, nodular appearance on stereoscopic viewing, orange retinal nodule, hypo fluorescent halo, pulsatile polyp or massive sub macular hemorrhage. (30)When ICG isn't available, clinicians can use alternative modalities like optical coherence tomography (OCT), en face OCT, and OCT angiography (OCTA). Figure 1B

OCT features

OCT findings suggestive of PCV include increased frequency of serous PEDs or increased height of the serous PED with less intraretinal fluid (IRF) as compared to lesions of similar size associated with exudative AMD.(31, 32) Figure 1C. A notch in the margin of a PED frequently indicates the presence of polyps. The BNV appears as two hyper reflective lines known as the “double layer sign”. The double layer sign reflects Bruch's membrane and RPE separated by the BVN.(31–33) PCV polyps are seen as a focal highly peaked elevation

of the RPE. The choroid is often thickened on enhanced-depth imaging OCT, frequently measuring >300 μm .(34)

En Face OCT

En face OCT is a software viewing option on most spectral-domain OCT machines. In order to image the polypoidal complex, the OCT image must include structures below the RPE and above Bruchs membrane using slabs of 10–30 μm thickness. The polypoidal complex is visualized as dilated vascular structures with hyper-reflective borders. There is a good correlation between en face OCT and ICGA in their sensitivity in identifying PCV complexes.(35–39)

Optical Coherence Tomography Angiography

A newer diagnostic innovation is the OCTA, which allows imaging of blood flow through the retinal and choroidal vasculature in a non-invasive fashion with a rapid acquisition time. There are limitations in OCTA including image quality being dependent on the flow of the BNV and inability not able to single out the complete PCV complex.(40, 41) Figure 1B

MEDICAL TREATMENT

Current Treatment plans can be formulated based on 3 pieces of information: the location of the PCV complex, the baseline vision and the response to previous therapy. Options available are photodynamic therapy (PDT), anti-VEGF therapy, combination of PDT and anti-VEGF and laser photocoagulation.

PDT

The results of the EVEREST clinical trial highlighted a higher rate of polyp closure with PDT alone or when combined with ranibizumab.(30) They found a greater polyp regression with PDT combined with ranibizumab (77.8%), followed by PDT alone (71.4%) and less closure with ranibizumab alone (28.6%).(30) The EVEREST-II and PLANET evaluated anti-VEGF and combination therapy. EVEREST II compared ranibizumab with combination of ranibizumab and PDT at baseline and PLANET, aflibercept with or without rescue PDT available after 3 months. Both studies showed a significant gain in visual acuity in the anti-VEGF monotherapy arm at 1 year. Polyp closure rates were 34.7% (EVEREST-II) and 38.9% (PLANET). The mean of injections was 7.3 for (EVEREST-II) and 8.1 (PLANET). (42, 43) A recently published analysis of the Japanese cohort of EVEREST II study over 12 months confirmed the same conclusion as in the 24 month-month study. The best available evidence suggests that combination therapy resulted in improved vision and achieved a higher rate of complete polyp regression with a lower number of anti-VEGF injections when compared with monotherapy.(44)

Our recommendations based on available study data to include PDT as art of treatment is based on the following:

1. If subfoveal or juxtafoveal PCV and

- a. Baseline vision worse than 20/40 PDT monotherapy or PDT plus anti-VEGF better than no PDT;
  - b. If vision 20/40 or better an intense and consistent treatment with anti-VEGF alone may be preferable because of the rare PDT complication of choroidal ischemia or subretinal hemorrhage.
2. Anti-VEGF alone can reduce serosanguinous complications in PCV.

ANTI-VEGF THERAPY

PCV has a less reliable response to anti-VEGF therapy than exudative AMD.(45) Aqueous humor of eyes with PCV contains high levels of VEGF when compared to controls but less than in eyes with exudative AMD.(46) In Asia, PDT has been the first line therapy for PCV while in the US, anti-VEGF is often first line treatment for serosanguinous maculopathy. Few retrospective studies with bevacizumab showed a low rate of polyp closure (21%).(47) Characteristics associated with better vision outcome such as smaller lesion, absence of PED at baseline and no CNV recurrences.(48)

The PEARL 1 study, a prospective, open-label clinical trial of monthly intravitreal ranibizumab injections (IRI) in 13 eyes showed statistically significant improvement in visual acuity and decrease in central foveal thickness (CFT) at one year. This study found a decreased volume of the PCV complexes in 38%, but an increase in 31% after one year.(49) When a higher dose of IRI was used (2.0 mg) in 19 eyes in the PEARL 2 study(50), there was a better response in polyp regression at 6 months (78.9% decreased polyps vs 21.1% stable), similar to EVEREST study results in the PDT subgroups. EVEREST II showed that combination therapy resulted in superior visual and angiographic outcomes at the same time reducing the need for repeat injections during the first year of treatment.

In the LAPTOP study, a prospective, multicenter randomized clinical trial comparing PDT with IRI showed a superior visual acuity in the IRI arm.(51) Recently long term visual acuity results in 29 eyes with PCV based on the first-choice treatment, either PDT or IVR concluding that the better VA in the initial IRI group compared with the PDT group at 2 years was retained at the 5-year follow-up.(52)

The EPIC study was a 6-month prospective open-label investigator-sponsored trial in 21 eyes that evaluated the treatment results of intravitreal aflibercept injections (IAI) for PCV with hemorrhage and exudation in eyes previously treated with ranibizumab and bevacizumab. At 6 months, vision was stable or improved in 19/21 eyes (91%). Subretinal fluid resolved in 72 % of the eyes, and subretinal hemorrhage resolved in 75 %. The polyps regressed in 67 % of the eyes and the BNV decreased in 1 eye only but was stable in all other eyes. The retinal pigment epithelial detachment (PED) improved in 87 % of the eyes. (53)

The 96-week multicenter randomized clinical trial PLANET study compared IAI monotherapy with IAI with rescue PDT. They all received initially monthly IAI for 3 months. Vision and/or functional outcomes was achieved in more than 85% of participants who were treated with IAI only, and no signs of leakage from polypoidal lesions in more

than 80%. The potential benefit of adding PDT could not be determined unfortunately since only fewer than 15% met the criteria of a suboptimal response to receive PDT.(43) Currently there is no evidence that adding PDT to aflibercept can give any additional benefit to the patient. If aflibercept is used, fixed dosing should be planned and patient prepared.

INTRAVITREAL STEROID THERAPY

There aren't studies comparing PDT combined with anti-VEGF and intravitreal steroids (triple therapy) to anti-VEGF monotherapy and/or PDT combined with anti-VEGF. A 2 year study comparing combined PDT and intravitreal triamcinolone to PDT monotherapy showed no visual significant difference at 2 years between the groups. (54) A retrospective study that compared PDT monotherapy to combination PDT and intravitreal bevacizumab and triamcinolone acetonide, showed that the combination therapy allowed for longer interval between treatments and better vision outcomes.(55) A recent prospective, consecutive case series of 17 eyes treatment naïve PCV of 13 patients were treated with a combination of PDT, intravitreal aflibercept 2 mg and intravitreal dexamethasone 600 µg/0.15 ml. The first dose of aflibercept and intravitreal dexamethasone were given on the same day, but separate, and followed by full fluence PDT. One year results showed that the majority of the eyes remained stable except for 2 eyes that needed re-treatment. Further studies are needed to compare monotherapy of different anti-VEGF agents with or without additional PDT, as well as to explore the value of adjuvant intravitreal steroids in order to decrease leakage since the side effects of steroids are always a concern.(56)

LASER PHOTOCOAGULATION

In some cases where lesions are extrafoveal standard laser photocoagulation therapy has been shown to effectively decrease exudation and induce regression of the polypoidal lesions improving VA and a long term resolution.(57) This option obviates some of the known risks and expenses of PDT and intravitreal anti-VEGF therapy, unfortunately in most cases PCV lesions extend too close to the fovea for this to be a viable treatment option.

TREATMENT REGIMEN AND MONITORING

If anti-VEGF monotherapy is chosen, the fixed dose (PLANET study) with 3 monthly aflibercept injections followed by 8 weekly injections should be adopted or if following a PRN regimen (EVEREST-II), 3 monthly ranibizumab injections followed by monthly monitoring with retreatment offered on a PRN basis.

If patient is receiving anti-VEGF alone and is responding suboptimal, consider reaped ICGA and add PDT if active polyps identified on ICGA.

A summary of the advantages and disadvantages of different treatment modalities are shown in Table 1.

CONCLUSION

There is no one optimal treatment strategy to treat PCV. Still, increasing awareness about the PCV diagnosis will lead to improved outcomes. Patients who present with significant decrease in final vision tend to develop degeneration and atrophy of the retinal pigment epithelium due to long standing macular serous fluid or hemorrhage. Anti-VEGF therapy can preserve visual outcomes when PCV is recognized early enough. Previous publications have shown a relatively favorable outcome in patients with good initial VA treated with anti-VEGF monotherapy. Due to the recurrent chronic nature of PCV, and increasing amount of intraretinal lipid after recurrences or as a consequence of persistent serosanguinous fluid, even after resolution atrophy and subretinal fibrosis often adversely affect final vision(21). The initial treatment can include anti-VEGF monotherapy as well as combination of anti-VEGF and PDT in patients with symptomatic PCV. EVEREST-II and PLANET studies were level I evidence that anti-VEGF therapy alone or combined with PDT can give excellent visual outcomes at 1 year. The treatment of choice if vision is 20/40 or better and polyps are located under the fovea, remains anti-VEGF whether or not combined with low fluence PDT. Short-term visual outcome is good, especially if treatment started early in the course of the disease and promising good or at least stable longer-term outcome if anti-VEGF was the choice to start treatment.(43, 49, 51, 52, 57) Given the response of the polypoidal complex to PDT, the decreased number of total injections the known phenomenon of anti-VEGF resistant cases of PCV adjuvant PDT can contribute to superior anatomical and visual outcome in some cases. Combination therapy might also be preferred if patient monitoring or adherence to retreatment is an issue. Each case of PCV treatment is unique and depends on the vision, location of polyps and the BVN, the degree of leakage and the response to anti-VEGF therapy.

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Figure 1 –.

(A) Left eye fluorescein angiography and indocyanine green (ICG) with several hyperfluorescent polypoid structures seen in the last phase of the ICG (arrow); (B) Optical coherence tomography angiography and optical coherence tomography spectral domain showing branching vascular network (*); (C) Large pigment epithelium detachment over area with polypoidal lesions with small amount of subretinal fluid.

Photo Credit: Luis Bernhard, CRA

TABLE 1.

Advantages and disadvantages of different treatment modalities for PCV

METHOD	PLUS	MINUS
Focal laser	Low cost Safe for extrafoveal or extramacular polyps Combination might be needed in recurrent cases	Scar Paracentral scotoma High recurrence rate Untreated BVN with persistent exudation
PDT	High rate of polyp regression (80%) Reduced fluency is safer Limited retreatments needed Stabilize vision in 80% Improve vision 25–55%	Long-term vision (2 years or more) return to baseline or decreases If repeated causes cumulative damage Rare cases of acute vision loss (subretinal hemorrhage, RPE tear and choroidal infarct) High cost
Anti-VEGF therapy	Favorable visual outcomes Not ICGA dependent	Limited polyp regression (25–40%) Multiple treatments High cost