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The Many Faces of Polypoidal Choroidal Vasculopathy

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Abstract

Introduction: Polypoidal choroidal vasculopathy (PCV) involves subretinal vascular lesions associated with serous and hemorrhagic retinal pigment epithelium detachments. It often presents in the macula as massive subretinal hemorrhage or orange nodules and less commonly in peripapillary or extramacular areas. PCV is often misdiagnosed as conditions that have different pathophysiology and treatment plans, such as exudative age-related macular degeneration or central serous choroidopathy. Case: This teaching case report discusses a patient with previously misdiagnosed peripapillary PCV. Multimodal imaging utilization and specialist consultations that led to the proper diagnosis are presented along with a review of the current evidence-based treatment guidelines. Results: In this case, the PCV lesions regressed after careful monitoring. Conclusion: Early recognition of PCV and an understanding of factors that influence recurrence can improve prognosis and management and co-management by optometrists.

Key Words: *polypoidal choroidal vasculopathy, choroidopathy, pachychoroid, retinal hemorrhage, ocular oncology, retinal pigment epithelium, indocyanine green angiography, optical coherence tomography*

Background

Polypoidal choroidal vasculopathy (PCV) is characterized by subretinal, vascular lesions associated with serous and hemorrhagic detachments of the retinal pigment epithelium (RPE). Typically, it presents as massive (greater than 4 disc diameters) subretinal hemorrhage or orange nodules in the macular area. It can also occur in the peripapillary and extramacular areas, albeit less often.[1] Other names given to this condition include “posterior uveal syndrome” and “multiple recurrent RPE detachment in black women.”[2] It is a variation of choroidal neovascular membrane (CNV); however, it has a different pathophysiology than CNV related to exudative age-related macular degeneration (AMD) associated with subretinal hemorrhage.[3,4]

PCV starts unilaterally but may later develop in the fellow eye. While it can be diagnosed in patients as young as 20 years, patients usually become symptomatic between age 50 and 65.[5] There is no definite male or female predilection; however, initial reports mentioned higher prevalence in middle-age women than in men, with an approximately 4.7:1 ratio.[1] Other studies from Japan report PCV is more common in Asian men than women.[6] It is more common in pigmented individuals including Blacks, Asians and Hispanics.[7] It may be present in 4%-10% of Caucasians with presumed AMD depending on the study, and in 23.9%-54.7% of Asian patients with presumed AMD.[8,9,11,12] Other risk factors for PCV have been identified as smoking, cardiovascular disease, hypertension and hyperlipidemia (similar to those of AMD). High body mass index also has been identified as a risk factor.[13]

While macular PCV is often misdiagnosed as exudative AMD or central serous choroidopathy, their

pathophysiology and treatment differ. Multimodal imaging is often necessary to distinguish between similarly appearing conditions. This teaching case report discusses a patient with PCV in the peripapillary area that was previously diagnosed as multiple other conditions. It presents the pathophysiology, retinal manifestations and most current diagnosis and evidence-based management guidelines for PCV. The target audience is optometry residents and third- and fourth-year optometry students.

Case Description

A 55-year-old African American male presented for his annual eye exam with no visual or ocular complaints. Medical history included remission of prostate cancer and longstanding headaches around his occipital lobe, which were monitored by a neurologist without treatment. Ocular history included pseudophakia of both eyes and an amelanotic lesion in the peripapillary area of the left eye. Family ocular history was unremarkable.

The retinal lesion of the left eye had been diagnosed as a retinal hamartoma 2 years prior by a retinal specialist **(Figure 1)**. One year after that diagnosis, the lesion had grown and begun to hemorrhage **(Figure 2)**. The retinal specialist then re-diagnosed the lesion as a retinal cavernous hemangioma and administered one injection of intravitreal bevacizumab (Avastin) at a standard dose of 1.25 mg in the left eye.

At the current visit, the patient's best-corrected visual acuity (BCVA) was 20/20 in each eye. Pupils reacted normally, ocular motilities were full in each eye and confrontation visual fields were full in each eye. Ocular motilities were full. Intraocular pressure with Goldmann applanation tonometry was 14 mmHg in the right eye and 15 mmHg in the left. Slit lamp exam was unremarkable and posterior chamber intraocular lenses were clear and centered in each eye.

Dilated fundus exam revealed an amelanotic lesion in the peripapillary area of the left eye with two associated hemorrhages: one was located superior-temporal and one superior-nasal **(Figure 3)**. On photographic review, it seemed the lesion had grown. The right eye's fundus evaluation was unremarkable. Cirrus optical coherence tomography (OCT) at the area of the lesion revealed the presence of enlarged pachyvessels with subretinal fluid **(Figure 4)**. More advanced OCT imaging was not available at the facility.

Given the patient's history of headaches and the growing lesion (now associated with retinal hemorrhaging), magnetic resonance imaging of the brain and orbits was ordered to rule out a space-occupying lesion. The results were normal. The patient was also referred to an ocular oncologist who ordered indocyanine green angiography (ICGA) and fluorescein angiography (FA) to properly diagnose the condition. ICGA revealed focal hyperfluorescent "polyps" during the early phase and leakage from "polyps" during the late phase, which was instrumental in the diagnosis **(Figure 5)**.

The patient was diagnosed with PCV in the left eye based on the fundoscopic and angiographic findings. The ocular oncologist recommended photodynamic therapy (PDT) alone or in combination with anti-vascular endothelial growth factor (VEGF) treatment in the future if the vision were to become affected. Fortunately, the lesion and the hemorrhages regressed with monitoring alone at the subsequent 3- and 6-month follow-up visits **(Figure 6)**. The retina specialist continued to monitor the patient without treatment.

Figure 1. Amelanotic lesion in the peripapillary region of left eye was identified 2 years prior and diagnosed as retinal hamartoma. Click to enlarge

Figure 2. 1 year after the first diagnosis, the lesion was re-diagnosed as retinal cavernous hemangioma. Click to enlarge

Figure 3. Apparent lesion growth and associated hemorrhaging observed at the current visit warranted referral to ocular oncology, which eventually led to a PCV diagnosis. Click to enlarge

Figure 4. Cirrus SD-OCT shows an enlarged pachyvessel (red arrow) and subretinal fluid (gray arrow). Click to enlarge

Figure 5. A) Early-phase ICGA shows focal polyps. B) Late-phase ICGA shows leakage from polyps. Click to enlarge

Figure 6. The regressed PCV lesion at the 3-month follow-up visit. Click to enlarge

Education Guidelines

This case report is appropriate for discussion among third- and fourth-year optometry students and would be most applicable to those in primary care or ocular disease rotations. The authors recommend presenting the case as a PowerPoint with concurrent verbal discussion. A slide presentation is ideal for step-by-step case review with graphics and ancillary test results. A parallel verbal discussion of the case report should incorporate **Table 1** and **Figure 7** as teaching tools. Table 1 aids in teaching proper classification and description of PCV lesions. Figure 7 is a tool for teaching PCV treatment and management recommendations. The verbal discussion should also include the discussion questions (below) to evaluate the learning objectives and student understanding of the condition, its management and treatment. The discussion questions should be completed once the case and discussion section of the paper have been thoroughly read and reviewed.

Key concepts

1. Identify demographics and epidemiology of PCV
2. Identify clinical presentation of PCV
3. Consider appropriate differential diagnoses
4. Review pachychoroid classification of retinal disease
5. Determine appropriate referral and treatment recommendations

Learning objectives

1. Identify the various types and clinical manifestations of PCV
2. Understand the ocular anatomy of the condition along with its classification on the pachychoroid spectrum
3. Identify testing needed to confirm the PCV diagnosis, specifically OCT, FA and ICGA
4. Understand how the recommended treatment correlates with the pathophysiology

Discussion questions

1. What clinical signs and patient symptoms would be expected in a case of PCV?
2. What additional testing would assist in the diagnosis of PCV?
3. What are the typical features of this condition on OCT, FA and ICGA?
4. What newer multimodal imaging features assist in diagnosis of PCV? How do they differentiate PCV from similar-appearing conditions such as exudative AMD?
5. What specialty referrals would you consider making if you suspect PCV? What is the role of the optometrist in co-managing this condition with a specialist(s)?
6. What is the current evidence-based treatment for PCV?

7. What is the prognosis for PCV?
8. What factors can influence the recurrence of PCV lesions after PDT?

Discussion

PCV was first described by Yannuzzi as peculiar polypoidal, subretinal, vascular lesions associated with serous and hemorrhagic detachments of the RPE in the macula.[1] Yuzawa reported two distinct subtypes of PCV. The first type has both feeder and draining vessels, also known as branching vascular network (BVN). The second type has few inter-connecting channels but no BVN. The former is termed polypoidal choroidal CNV; the latter is termed typical PCV. He described polypoidal CNV as a deformation of the CNV under the RPE. In contrast, typical PCV without BVN is characterized by hyalinized arteriolosclerosis of choroidal vessels. Vitrectomy of a typical PCV eye shows massive exudative change in blood plasma and basement membrane-like deposits of slight granulomatous tissue beneath Bruch's membrane.[4]

Genetic studies have linked subtypes of PCV to particular genes. Complement factor H and age-related maculopathy susceptibility (ARMDS2) gene is seen in Japanese and Caucasian patients with polypoidal CNV, but not in typical PCV.[4] Both these genes are strongly associated with exudative AMD.[4,14,15] Tanaka and associates suggested complement component-2 and complement factor B gene variants might be possible genetic markers for polypoidal CNV, but not typical PCV.[16] These genes are known activators of alternative complement cascade in Caucasian patients with AMD. Despite these genetic similarities between AMD and PCV, differences in susceptibility patterns have been identified and can aid in proper diagnosis.[17]

Studies have also reported an upregulation of VEGF and pigment epithelial derived factor in the aqueous humor of eyes with PCV.[18,19] This change might be responsible for the neovascular complexes seen in PCV. These factors are prominent in active CNV and less common in new vessels where fibrosis or quiescent CNV was prominent.[17]

On dilated fundus exam, the dilated inner choroidal vessels of a PCV lesion appear as multiple reddish-orange nodules beneath the RPE.[20] According to Tan, there is a predilection for the macular region at 87.5%, and less frequent presence in the peripapillary region (6.5%) and extramacular region (5.6%). In the aforenoted study, macular region was defined as within 2 disc diameters (or 3 mm) from the center of the fovea. Peripapillary region was defined as within 1 disc diameter from the optic disc margin. Extramacular region was considered anywhere outside the peripapillary and macular region. PCV lesions can be single and isolated or widespread and multiple.[21]

Table 1. Click to enlarge

It is not uncommon to see spontaneous massive subretinal hemorrhages due to the rupture of the thin-walled choroidal vessels. Hence, PCV lesions can also be classified clinically as quiescent, exudative or hemorrhagic. Quiescent is when there are polyps but no subretinal or intraretinal fluid or hemorrhage. Exudative is when there are no hemorrhages but some exudative changes such as sensory retinal thickening, neurosensory detachments, pigment epithelium detachment (PED) and subretinal lipid exudation. Hemorrhagic is defined as any subretinal or sub-RPE hemorrhage with or without other exudative changes.[22]

PCV has been categorized as part of the pachychoroid spectrum of retinal conditions. This group of conditions, in addition to PCV, includes central serous chorioretinopathy, pachychoroid pigment epitheliopathy and pachychoroid neovasculopathy.[23] Pachychoroid refers to a thickening of the choroid with characteristic pathogenic dilation of blood vessels in Haller's layer. These vessels are referred to as

"pachyvessels" and are associated with an abnormal increase in choroidal permeability.[24] Additionally, these pachyvessels are often accompanied by thinning of the choriocapillaris and middle choroidal layer vessels that overlie them. These features help to distinguish PCV from similarly appearing exudative AMD cases because the choroidal thickening pattern typical of pachychoroid is not associated with exudative AMD. In addition, there are minimal to no drusen associated with PCV, and there are often drusen associated with AMD.[23]

Diagnostic testing

OCT is a valuable, non-invasive imaging modality appropriate in PCV cases. On OCT, PCV lesions appear as chronic multiple "serosanguineous" detachments of the RPE and/or neurosensory retina.[25] Sato and associates observed a classic appearance of a "double layer sign" seen in 59% of eyes with PCV on OCT. It is seen as two highly reflective lines, one in the RPE and the other in the Bruch's membrane. It signifies the location of the BVN or choroidal vascular network.[26] According to the Asia-Pacific Ocular Imaging Society PCV Workgroup, a combination of three specific OCT findings supports a diagnosis of PCV: sub-RPE "ring-like" lesions, en face complexes of RPE elevation, and sharp-peaked PEDs. The ring-like lesions appear as round structures underneath PEDs with varying levels of reflectivity; the en face RPE complexes appear as multiple PEDs connected by a hyper-reflective vascular network; and the sharp-peaked PEDs appear as "thumb-like" protrusions with steep vertical inclines. When using these three findings as diagnostic criteria, an accuracy level higher than 80% was achieved.[27]

The advancements in OCT technology have allowed for enhanced depth (ED) analysis of the choroid. The pathognomonic polypoidal lesions of PCV have been more specifically localized to a space between the RPE and Bruch's membrane. ED-OCT has been used to identify features that distinguish PCV from exudative AMD. The presence of increased choroidal thickness in eyes with PCV vs. those with AMD suggests different pathologies. Swept source OCT (SS-OCT) of pachychoroid patients has demonstrated that there is not always choroidal thickening; some patients classified as pachychoroid may have normal or even decreased choroid thickness due to concurrent atrophy of choroidal vasculature. SS-OCT also demonstrated that the area of maximal choroidal thickness in pachychoroid patients does correspond to the area with the greatest concentration of pachyvessels even if that maximum thickness level is not very high.[17]

OCT angiography (OCTA) is also useful in PCV diagnosis. A study by Chan et al. evaluated 31 patients with a total of 72 PCV lesions confirmed with ICGA. It was found that all lesions identified by ICGA were consistently identifiable on OCTA. Additionally, 53 of 72 lesions showed "cluster-like" structures on en face imaging of the relevant layers, and 50 of 72 demonstrated "internal channels of flow" on cross-sectional imaging. The larger the lesion was, the more likely it was to have the aforenoted OCTA appearance.[28] Srour also found that branching vascular networks could be reliably identified using this non-invasive imaging modality.[29] When OCTA was used to classify features of BVN, three main patterns emerged. A trunk-like pattern was most frequently observed, in about half of cases, followed by a "glomeruli-like" vascular network and a "stick" pattern.[30]

On FA, a quiescent PCV lesion typically has some occult CNV characteristics with early hyper- and hypofluorescence. Exudative lesions are observed as progressive and uniform hypofluorescence in the early phase with intense pooling in the late phase. Hemorrhagic lesions are hypofluorescent secondary to blockage of dye by blood. Hence, macular PCV is often misdiagnosed as occult or minimally classic AMD based on FA alone.[10]

ICGA is the gold standard for diagnosing, classifying and treating PCV. Indocyanine green absorbs and emits near-infrared light and is therefore able to penetrate RPE deeper. The dye also has a higher binding affinity to plasma protein, so it does not leak as rapidly from the choriocapillaris as

fluorescein.[30] ICGA should be considered whenever ophthalmic examination reveals spontaneous, massive subretinal hemorrhage, notches or hemorrhagic or serous PED, a lack of response to anti-VEGF therapy, and/or clinically visible orange-red subretinal nodules. However, appearance of orange-red nodular elevations is not diagnostic for PCV because small PEDs without polyps can have a similar appearance.[20]

In early- to mid-phase ICGA, larger choroidal vessels fill with dye while the surrounding area remains hypofluorescent. The “polyps” in terminal vessels, aneurysmal dilations, become hyperfluorescent prior to the retinal vessels. Leakage from the “polyps” begins during the mid phase. During this phase, the size of the choroidal hyperfluorescence matches the clinical observation of the lesion. During the late phase, the previously surrounding darker areas become hyperfluorescent while the center of the lesion becomes hypofluorescent. In the very late phase, a non-leaking PCV lesion will become “washed-out,” but a leaking PCV lesion remains hyperfluorescent.[32]

According to evidence-based guidelines for diagnosis of PCV by Tan, PCV is defined as single or multiple focal nodular areas of hyperfluorescence from choroidal circulation within 6 minutes after injection of indocyanine green with one or more of the following features (statistics in parenthesis represent prevalence of the relative factor):

- nodular appearance on stereoscopic view of ICGA (95.3%)
- hyperfluorescent halo surrounding the focal hypofluorescence (81.3%)
- association with BVN on ICGA (77.6%)
- pulsatile filling of the polyps in dynamic ICGA (25.2%)
- focal hyperfluorescence corresponding in location to an orange nodule of fundus (37.4%)
- association with massive (> 4 disc diameters) submacular hemorrhage (7.5%)[21,22]

Multiple reports have also suggested that pulsatile hyperfluorescent filling of the polyp nodule might be unique to PCV.[33-35]

Treatment/management

Treatment of PCV is based on location of active leakage and whether it is affecting vision. 50% of lesions are self-limiting and not visually significant.[20] PCV is considered active if any of the following are present: ophthalmic findings, OCT and/or angiography that attributes PCV to a drop in vision of at least 5 letters (on ETDRS chart), subretinal fluid with or without intraretinal fluid, PED or subretinal hemorrhage, or angiographic evidence of leakage.[22] 60% of active lesions will have complete resolution of serous retinal detachment when laser photocoagulation is applied to ICGA-identified polypoidal feeder vessels.[36] Therefore, active extrafoveal exudative leakage should be treated with laser photocoagulation. Active subfoveal and juxtafoveal PCV lesions are considered sight-threatening and should be treated based on the guidelines established by the EVEREST, EVEREST II and PLANET studies.

Figure 7. Adapted from evidence-based guidelines.[23,38] Click to enlarge

The EVEREST study was a multicenter, double-masked, prospective study investigating symptomatic PCV cases treated with verteporfin PDT combined with ranibizumab (Lucentis) vs. PDT alone vs. ranibizumab monotherapy. At 6 months, 71.8% of patients had complete regression with verteporfin PDT treatment alone with BCVA improvement of 7.5 letters, whereas 77.8% had complete regression with PDT verteporfin combined with ranibizumab with a 10.9 letter improvement. Ranibizumab monotherapy had a complete regression rate of 28.6% and improvement of 9.2 letters. Based on EVEREST findings, subfoveal and juxtafoveal PCV should be treated either with ICGA-guided verteporfin PDT or a

combination of verteporfin PDT and three 0.5-mg ranibizumab intravitreal injections at monthly intervals.[20] The results proposed that combination therapy should be considered the treatment of choice in the following scenarios: leakage from BVN and polyps, large amounts of subretinal fluid or exudation associated with PED, ICGA features that are ambiguous between PCV and CNV, and/or if the lesions are a combination of typical PCV and typical CNV. Ranibizumab monotherapy is suggested for initial therapy if verteporfin PDT treatment is contraindicated or not possible.[22] Subfoveal and juxtafoveal PCV should be monitored 3 months after initial treatment using FA, OCT and ICGA. If there is still leakage on FA/OCT but complete polyp regression on ICGA after 3 months, retreatment with ranibizumab is recommended. If there is incomplete regression of polyps, retreatment with verteporfin PDT monotherapy combined with ranibizumab or alone is recommended.[22]

The follow-up study, EVEREST II, investigated the safety and efficacy of ranibizumab monotherapy vs. combination therapy with ranibizumab and PDT in treating PCV. Participants were randomized into one of two treatment groups, ranibizumab plus PDT or ranibizumab with sham PDT, and monitored for 24 months. The average BCVA improvement in the combination therapy group was 9.6 letters as compared to the monotherapy group improvement of 5.5 letters. 56.6% of polyp lesions had complete regression in the combination therapy group as compared to 26.7% in the monotherapy group (which was consistent with findings in EVEREST). The results suggest that combination therapy with ranibizumab and PDT remains the superior treatment option over ranibizumab monotherapy.[37]

The PLANET study investigated the safety and efficacy of aflibercept (Eylea), with and without PDT in treatment of PCV. All patients received treatment with intravitreal aflibercept for the first 3 months, then were randomized into an aflibercept monotherapy group or a group qualifying for “rescue” PDT, which was subdivided into a sham PDT group and a rescue PDT group. After 52 weeks, mean improvement in BCVA for the aflibercept monotherapy group was comparable to the aflibercept plus PDT rescue group at 10.7 vs. 9.1 letters respectively. The proportion of patients with polyp regression after treatment was also comparable in the two groups with 33.1% regressed after aflibercept monotherapy and 29.1% regressed in the aflibercept plus rescue PDT group. This study concluded that aflibercept monotherapy was at least as effective for most PCV patients as combination therapy and additional treatment with rescue PDT did not offer a significant benefit.[38]

It has been noted that presence of a BVN tends to offer a less efficacious response to PDT as compared to lesions without BVN because of increased likelihood of recurrence. BVNs tend to leak even if the polyps themselves have completely regressed with PDT treatment. Hence, polypoidal CNV tends to have poorer prognosis for visual outcomes.[22]

The case at hand can be evaluated using the adapted evidence-based guidelines in **Figure 7** and the OCT features discussed above. Fundoscopic features of orange-red subretinal nodules along with spontaneous subretinal hemorrhage were present along with OCT features of pachyvessels and subretinal fluid. ICGA identified focal filling of polyps along with hypofluorescence matching the orange nodules seen on retinal exam. The level of leakage and its impact on vision were considered to determine treatment. Fortunately for this patient, the lesion was located near the optic nerve rather than at or near the macula and therefore close monitoring was the management of choice.

Conclusion

PCV is a commonly misdiagnosed condition. Guidelines for its management differ from those of similar-appearing conditions such as exudative AMD; therefore, initial proper diagnosis provides patients with the best opportunity for successful treatment. PCV is also a condition that can spontaneously regress or recur (if it has an associated BVN). This relapsing-remitting nature of PCV makes management challenging. Most often, PCV can be monitored. However, if the lesion is visually significant, ICGA-guided PDT with verteporfin in combination with anti-VEGF treatment should be utilized until the lesion

has regressed. The presence of BVNs increases recurrence rate and decreases prognosis of polypoidal CNV compared to typical PCV.

It is important for optometrists to understand the pathophysiology and progression of PCV to properly diagnose the condition, coordinate specialist referrals and counsel patients on prognosis. Such understanding also provides optometrists with increased ability to co-manage PCV patients undergoing treatment or monitor patients in whom treatment is not indicated. Lastly, this provides an opportunity for optometrists to provide rehabilitative and low vision services if the condition becomes visually significant enough to impede a patient's activities of daily living.

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