POLYPOIDAL CHOROIDAL VASCULOPATHY

It is crucial to distinguish this entity from neovascular AMD; treatment burden can be reduced if appropriate therapy is applied.

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Neovascular age-related macular degeneration (AMD) is a leading cause of blindness in the developed world.[1] Polypoidal choroidal vasculopathy (PCV), which presents as a serosanguinous maculopathy, is a variant of neovascular AMD.[2] Recently PCV has been described as a type 1 choroidal neovascularization (CNV) with or without a branching vascular network and with polypoidal dilated vessels located between the retinal pigment epithelium (RPE) and Bruch membrane.[3] Progression to severe visual acuity loss occurs in 50% of patients secondary to repeated episodes of exudation, hemorrhage, and scarring.[4,5]

PCV is increasingly becoming recognized globally, and its clinical presentation varies among ethnic populations. PCV more commonly presents unilaterally and in the macula of Asian men, and is more characteristically found in the peripapillary areas of white and black women with bilateral involvement.[6,7]

It is important to make the distinction between neovascular AMD and PCV because treatment approaches may vary. In Asian populations, between 20% and 50% of macular exudation and hemorrhage are found to have PCV.[8] In a recent Brazilian study in which the majority of patients with neovascular AMD were of European descent, 24.5% had PCV diagnosed on indocyanine green angiography (ICGA) at initial diagnosis.[9] A Swiss study of neovascular AMD refractory to ranibizumab (Lucentis, Genentech) therapy found that 21.5% of patients had the PCV variant, not neovascular AMD.[10]

This article reviews the imaging modalities for diagnosing PCV and the treatment options available for patients with PCV.

IMAGING PCV

On fundus examination, PCV usually presents with subretinal fluid and subretinal hemorrhage or hemorrhagic pigment epithelial detachment (PED) that is indistinguishable from neovascular AMD. Occasionally, orange-red subretinal vascular structures are seen to be associated with the subretinal hemorrhage or fluid and PED.[2] PCV is further defined on ICGA as an abnormal subretinal vascular complex, often with a branching vascular network (BVN) and polypoidal dilations appearing as a nodular hyperfluorescence, often with a hypofluorescent halo, and rarely as a pulsatile lesion.

ICGA is the essential modality for diagnosis of PCV.[11,12] In the United States, ICGA is not routinely ordered at the initial visit in patients presenting with serosanguinous maculopathy, a practice that contributes to the underdiagnosis of PCV.[13] ICGA is not always available; if it is not, clinicians may consider evaluating alternative imaging modalities such as optical coherence tomography (OCT), en face OCT, and OCT angiography (OCTA).

OCT

On OCT, the polyps of PCV complexes are defined by a focal highly peaked elevation of the RPE (an elevation shaped like an inverted U). Additionally, there are often associated serous retinal detachments (RDs), and the branching vascular network has a characteristic appearance as two hyperreflective lines on OCT that is termed the double-layer sign.[14-16] Distinguishing findings on OCT that suggest a PCV diagnosis include increased frequency of serous RDs,

AT A GLANCE

- PCV is a variant of neovascular AMD that presents as a serosanguinous maculopathy.
- PCV varies clinically in presentation among ethnic populations.
- ICGA is essential for the diagnosis of PCV.
- PCV complexes may be less responsive to anti-VEGF therapy than neovascular AMD; PDT may help to ease treatment burden.

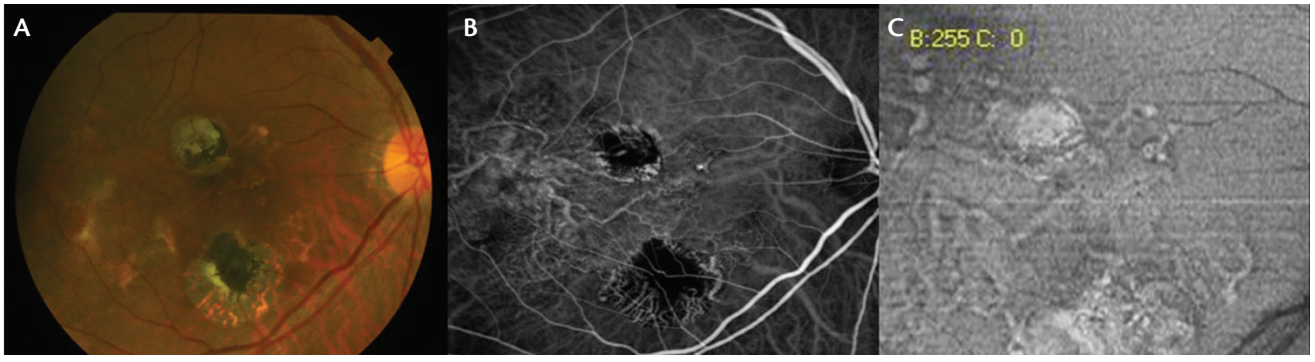

Figure 1. A Filipino-Asian woman with PCV in her right eye that was previously treated with macular laser for extrafoveal polyps has a large polypoidal complex in the central and temporal macula of her right eye. Superior and inferior RPE scars from prior focal laser to extrafoveal polyps are seen in a fundus photo (A). ICGA shows a large BVN and nasal polyp (B), and en face OCT shows characteristic PCV complex in greater detail and extent than ICGA (C).

increased height of the serous RD, and less intraretinal edema than is seen with neovascular AMD.[14,17] A thicker choroid is also noted on enhanced-depth imaging OCT in patients with PCV.[18]

En Face OCT

En face OCT is another noninvasive way to image PCV complexes (Figure 1). This is a software viewing option available on most spectral-domain OCT devices. To image the PCV complex, it is ideal to scan below the RPE and above Bruch membrane using slabs of 10 µm to 30 µm.[19] On en face OCT, the complexes are seen as dilated vascular structures with hyperechogenic borders. PCV complexes may appear larger on en face imaging due to the ability of this technique to detect areas that may have no flow and due to the imaging of tissue draped over and around the PCV vessels. Studies have shown good correlation of en face OCT and ICGA in their ability to identify PCV complexes.[19-23]

OCTA

Technology in retinal imaging is rapidly changing with new diagnostic innovations. OCTA is a new modality that allows imaging of blood flow through the retinal and choroidal vasculature. OCTA offers advantages over traditional ICGA and fluorescein angiography because it is noninvasive and has a rapid acquisition time. Few studies have confirmed the location of the PCV complex using OCTA, and, to date, OCTA is less frequently able to identify the complete PCV complex than other imaging options. A BVN with higher flow is better visualized than polyp lesions with lower flow (Figure 2). Further studies and continuing improvement in software will lead to better definition of PCV characteristics on OCTA in the future.[24,25]

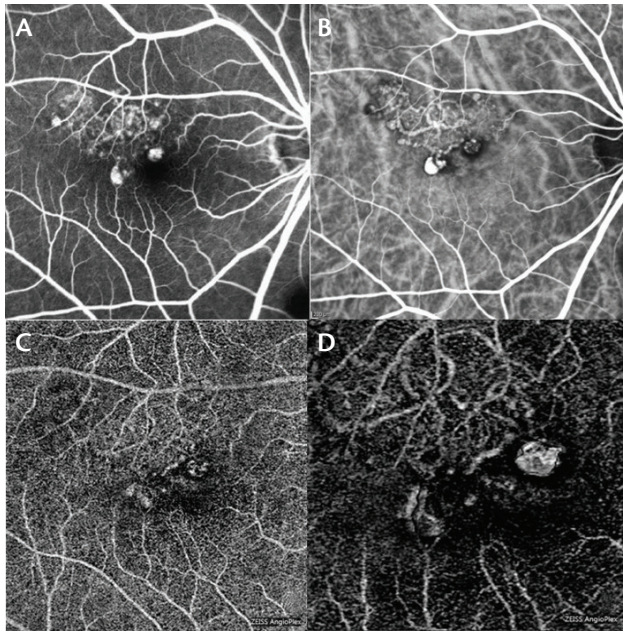

Figure 2. An Asian woman with PCV in her right eye had previously received anti-VEGF therapy. Fluorescein angiogram shows focal areas of leakage but poor vascular details (A). ICGA displays excellent vascular detail of BVN and polyps (B). OCTA 6 x 6 scan (C) and 3 x 3 scan (D) shows some flow in regions between the RPE and the Bruch membrane, but poor vascular detail compared with ICGA.

TREATMENT

Treatment of PCV is complex and based on visual acuity, location of the PCV complex, and response to therapy. Various treatment options for PCV exist, including photodynamic therapy (PDT), anti-VEGF therapy, and laser photocoagulation.

PDT

One of the landmark studies in PCV treatment is the prospective EVEREST clinical trial, which compared PDT alone, anti-VEGF therapy alone, and PDT in combination with anti-VEGF therapy.[26] That study found that polyp regression was greatest with PDT in combination with ranibizumab, followed by PDT alone and ranibizumab alone, with polyp closure rates of 77.8%, 71.4%, and 28.6%, respectively.[26]

A roundtable expert panel on PCV treatment concluded that, in subfoveal and juxtafoveal PCV, PDT alone or in combination with anti-VEGF treatment should be the first-line treatment.[27] However, due to concern for the rare complications of choroidal ischemia or subretinal hemorrhage, PDT is often not used in eyes with subfoveal lesions with good visual acuity of 20/40 or better. Anti-VEGF therapy alone can reduce serosanguinous complications in PCV, but it has limited efficacy in causing PCV complex regression (Figure 3).

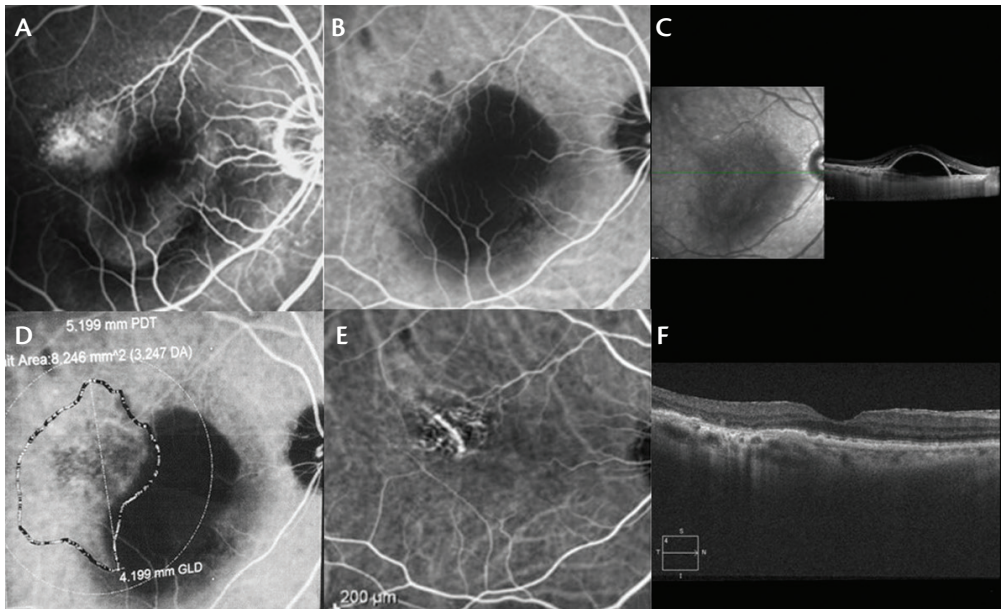

Figure 3. PCV presented with a vascularized RPE detachment (RPED) in an Asian male with initial visual acuity of 20/60. Fluorescein angiogram shows RPED with superotemporal occult leakage (A), and ICGA shows superotemporal PCV network. Note the dark hypofluorescent area corresponding with the RPED on the scanning laser ophthalmoscopic image (B). Corresponding OCT shows RPED and nasal serous detachment (C). The region of the visible PCV complex was mapped, and the size of PDT treatment was the greatest linear dimension with an additional 300 µm border (D). Posttreatment ICGA shows resolution of the PCV complex and the RPED (E), and corresponding OCT confirms resolution of the RPED and serous detachment (F). Visual acuity was 20/30 at 32 months after one PDT treatment and three subsequent intravitreal injections of a combination of bevacizumab and dexamethasone. No treatment has been necessary for more than 2 years.

Anti-VEGF Therapy

Although PDT is the mainstay therapy for PCV in Asia, anti-VEGF therapy is more often first-line treatment for serosanguinous maculopathy in the United States. Retrospective studies with bevacizumab (Avastin, Genentech) to treat PCV show a low rate of polyp closure (21%) but some improvement in visual acuity and anatomic changes within the retina.[28]

In the PEARL 1 study, a prospective, open-label clinical trial of monthly ranibizumab, PCV complexes were decreased in 38% of patients, stable in 31% of patients, and increased in 31% of patients at 1 year. There was a statistically significant improvement in visual acuity and a decrease in central foveal thickness in this cohort of 13 eyes.[29]

The LAPTOP study, a prospective, multicenter randomized clinical trial comparing PDT with ranibizumab, reported superior visual acuity outcomes in the ranibizumab arm.[30]

High-dose (2.0 mg) ranibizumab therapy was prospectively studied in 19 eyes in the PEARL 2 trial.[3] At 6 months, 26% of patients had a statistically significant improvement of visual acuity. The polyps in this study decreased in 78.9% of eyes and were stable in 21.1% of eyes.[3] This study showed a better response in polyp regression with high-dose ranibizumab than the standard dose of ranibizumab, which was similar to the responses seen in PDT subgroups in the EVEREST study. Given the differences in the studies, however, they cannot be directly compared.

The anti-VEGF agent aflibercept (Eylea, Regeneron) has also been used to treat PCV. In a 1-year retrospective review of patients with treatment-naïve PCV, aflibercept was noted to significantly improve vision and decrease central foveal thickness and to cause PCV complex regression in 66% of patients at 3 months. Twenty-six percent of those patients who had complete polyp regression at 3 months had recurrence of the polypoidal lesion at 1 year. This finding shows that polypoidal lesions must be watched, even in eyes in which lesions have regressed, and it highlights the complexity of managing this disease entity.

PCV is less responsive to anti-VEGF therapy than is

neovascular AMD. In patients who were initially diagnosed with neovascular AMD but were poor responders to anti-VEGF treatment, ICGA has revealed a diagnosis of PCV, prompting the use of PDT and thus decreasing the burden of intravitreal injections with an improvement in anatomic and visual outcomes.[31,32]

Laser Photocoagulation

Laser photocoagulation has been used to treat extrafoveal polyps associated with subretinal hemorrhage and subretinal fluid. It has been shown to decrease exudation and cause regression of the polypoidal lesions with improvement of visual acuity, which can result in long-term resolution of polyps that are safely away from the fovea. However, in most cases the polyps and the BVN complex leak, and, if the lesion extends too close to the fovea or through the fovea, then laser photocoagulation is not an option due to the underlying damage to the retina and RPE, which can result in permanent visual acuity loss.[33]

INCREASING AWARENESS, IMPROVING OUTCOMES

PCV is increasingly being recognized by practitioners globally as awareness is raised about the diagnosis and treatment of this disease. It is less frequently recognized in locations where ICGA is not available or is underutilized and where PDT has become less frequently used due to a lack of access to the lasers or the personnel needed to perform the procedure. En face OCT provides an alternative imaging method to make the diagnosis of PCV, and OCTA is a developing new technology that will allow better imaging of flow in subretinal neovascularization.

The treatment of PCV is complex, with a treatment paradigm that differs from that of neovascular AMD. Given the response of the polypoidal complex to PDT, the decrease in burden of anti-VEGF treatment with PDT therapy, and the resistance, in some cases, of PCV complexes to anti-VEGF agents, superior anatomic and visual outcomes in PCV can be achieved with PDT. This makes each case of PCV treatment unique, depending on the location of polyps and the BVN, the degree of leakage from the polyps and BVN, and the response to anti-VEGF therapy.

With the use of other diagnostic modalities to diagnose PCV, and with the recognition of this disease entity as a subtype of subretinal neovascularization with higher anti-VEGF resistance, treatment outcomes can be improved with less treatment burden in the future. ■

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