Editorial

Polypoidal Choroidal Vasculopathy—An Important Diagnosis to Make with Therapeutic Implications

Polypoidal choroidal vasculopathy (PCV) is an increasingly recognized cause of exudative and hemorrhagic complications in the macula.[1–3] This exudative maculopathy mimics all the findings of exudative age-related macular degeneration (AMD) on clinical examination and fluorescein angiography. Indocyanine green (ICG) angiography is required to accurately identify PCV, which manifests as hyperfluorescent polypoidal lesions with or without a visible branching vascular network.[4]

Although recent discussion has focused on whether ICG angiography is still relevant,[5] ICG angiography remains necessary and essential for the diagnosis and management of PCV.[4,5] Even though a widely accepted criterion for the definition of PCV based on ICG angiography is yet to be developed, the need for ICG angiography to make the diagnosis of PCV is widely accepted. Despite this widespread acceptance of ICG angiography to diagnose PCV, ICG angiography is not widely used in many countries, except in Asian countries, where PCV prevalence is especially high.

Polypoidal choroidal vasculopathy occurs in all ethnic groups, including white populations,[6,7] although it is seen more commonly in Asian[8,9] and African American populations.[10] Because it occurs in all populations, PCV would be more frequently diagnosed with increased use of ICG angiography in all patient populations. Because ICG is not routinely done in white populations, the true incidence of PCV in whites is still unknown, although it is suspected to be higher than previously reported.

Although it is controversial whether PCV is a choroidal vascular abnormality, or whether PCV is a type of subretinal neovascularization,[3,7,11] recently there is increasing evidence that PCV is a type of subretinal neovascularization growing between the retinal pigment epithelium (RPE) and Bruch membrane or within Bruch membrane.[11] This represents a variant of type I subretinal neovascularization, as previously defined by Gass[12] and more recently updated by Freund et al.[11]

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Histopathology has also confirmed that PCV represents large, thin-walled, cavernous vascular channels with accompanying choroidal neovascularization within Bruch membrane and underneath the RPE.[13,14]

En face optical coherence tomography studies have shown that polypoidal choroidal vasculopathy results in small round protrusions of the RPE, while the branching vascular network induces slight elevation of the RPE from the underlying Bruch membrane.[15] C-scan en face spectral optical coherence tomography has shown that PCV lesions are often contiguous with subretinal neovascularization located between the RPE and Bruch membrane.[7] Since the PCV vessels are beneath the RPE, and also are more mature vascular structures than choroidal neovascularization associated with exudative AMD, this may have implications in regards to the response to different therapeutic modalities.

In a recent issue of *Retina*, Koh et al[16] found in a randomized controlled clinical trial (EVEREST study) a much higher polyp closure rate with photodynamic therapy (PDT), or combined PDT and ranibizumab, when compared with ranibizumab monotherapy alone. These findings highlight the importance of making the diagnosis of PCV with ICG angiography, as PDT may represent an important part of the therapeutic regimen for PCV. In addition, in the EVEREST study, ICG angiography actually guides therapy with PDT, as it was used to show the location of the polypoidal vessels and to minimize spot size by localizing PDT only to the area of the PCV vessels on ICG angiography.

Diagnosing PCV may also be important for evaluating and guiding therapy outside of PDT. Antiangiogenic therapy with anti–vascular endothelial growth factor (anti-VEGF) drugs has become the mainstay of treatment for exudative AMD, resulting in significantly improved visual and anatomical results than any previously available therapy. Treatment for PCV with anti-VEGF drugs has been studied with bevacizumab and ranibizumab. In retrospective studies, bevacizumab was found to lessen the amount of exudation but not as successfully as previously reported in

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exudative AMD.[3,17,18] In addition, eyes documented to have PCV on ICG angiography have been recently recognized to be sometimes refractory to anti-VEGF therapy and thus more resistant to bevacizumab or ranibizumab.[19,20]

Prospective trials using ranibizumab for PCV are available from the recent ranibizumab monotherapy group of the EVEREST trial[16] and the PEARL trial.[17] Although exudation and hemorrhage resolved on monthly therapy, polyp regression occurred only in 28.6% of the EVEREST trial and 33% of the PEARL trial. Although anatomical regression of polypoidal lesions was much less frequent than treatment regimens including PDT, visual acuity improved significantly ≥15 letters in 33% of EVEREST patients at 6 months and in 17% of PEARL patients at 6 months on monthly ranibizumab therapy. Mean letters of visual acuity gain after 6 months of ranibizumab therapy was 9.2 letters in the EVEREST trial and 7.2 letters in the PEARL trial. Baseline visual acuity was worse in the PEARL trial (mean 43.8 letters) than in the EVEREST trial (mean 49.0 letters). After 1 year of continuous monthly therapy in the PEARL trial, 23% of patients had improvement by ≥15 letters (unpublished data; presented at the European-American Symposium on AMD, Euretina Annual Meeting, London, England, May 29, 2011). When compared with the MARINA trial results with monthly ranibizumab at 1 year, in which 33.8% of patients improved by ≥15 letters,[22] this is significant visual improvement but not as robust as the treatment response seen in exudative AMD and occult choroidal neovascularization (CNV).

Photodynamic therapy has been the mainstay of treatment for PCV for many years. The EVEREST study showed a much higher rate of polyp regression with PDT in 71.4%, and with combined PDT and ranibizumab in 77.8%, compared with ranibizumab monotherapy in 28.6%. Although these anatomical results are strongly in favor of PDT as part of the treatment regimen for PCV, the visual results were not statistically different among the three groups. Although not powered to detect visual acuity differences between treatments, patients gaining ≥15 letters were 33.3% in the ranibizumab-only group, 21% in the verteporfin PDT + ranibizumab group, and 19% in the verteporfin PDT monotherapy group. Thus, at present, it is unknown if anatomical resolution of polyps changes visual acuity outcomes.

When visual acuity is good, then eyes with PCV respond best to anti-VEGF therapy with the best vision results. In Japanese patients treated with ranibizumab, there was more likely to be visual improvement in PCV eyes than in AMD eyes.[23] In addition, better visual acuity at baseline correlated with a better visual outcome on ranibizumab therapy for at least 1 year.[23] Because these eyes with better baseline visual acuity have good useful vision, PDT may be more likely to be avoided because of the rare risk of acute vision loss with PDT, most commonly due to subretinal or sub-RPE hemorrhage[24] or due to choroidal nonperfusion.[25,26]

However, when visual acuity is poor in eyes with PCV, or when there is poor response to anti-VEGF therapy, then therapeutic regimens, including PDT for PCV, become important to consider. Indocyanine green angiography can be used to diagnose PCV and then to guide PDT therapy to the location of the polypoidal vessels. Photodynamic therapy with or without anti-VEGF therapy may have a higher chance of closure of subretinal vessels and of decreasing the number of needed retreatments compared with anti-VEGF monotherapy.

To make therapeutic decisions for eyes presenting with hemorrhagic and exudative complications in the macula, ICG angiography is an important diagnostic study to consider because it is the only reliable way to diagnose PCV. Once PCV is diagnosed, then anti-VEGF therapy may still be considered because of a good chance of resolution of exudative and hemorrhagic complications in eyes with good vision. Photodynamic therapy may be considered more strongly once PCV is diagnosed, and if visual acuity worsens, or if there is resistance to anti-VEGF therapy. Since the PCV vessels are under the RPE, there is also a possibility that higher doses of existing drugs or increased penetrating ability of new drugs through the RPE may allow a more significant medical therapeutic effect on the PCV vessels. Studies with higher doses of ranibizumab (1.0–2.0 mg) are currently under way at The Retina Center at Pali Momi to investigate the effect of higher doses of ranibizumab.

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