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MANAGING ANTI–VEGF-RESISTANT NEOVASCULAR AMD: IS IT POLYPOIDAL CHOROIDAL VASCULOPATHY?

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ACTIVITY DESCRIPTION

Anti–vascular endothelial growth factor therapy is the clinical standard for first-line therapy of neovascular age-related macular degeneration. Although this therapy benefits many patients, a subset of patients responds poorly or not at all. Misdiagnosis is one reason. A commonly overlooked diagnosis is polypoidal choroidal vasculopathy, a variant of neovascular age-related macular degeneration that does not consistently respond well to anti–vascular endothelial growth factor therapy. The perception that polypoidal choroidal vasculopathy occurs rarely is changing. Photodynamic therapy is the most widely published treatment for polypoidal choroidal vasculopathy and is an important part of initial treatment. Many retina specialists, however, lack knowledge of the role photodynamic therapy can play in response to suboptimal response to anti–vascular endothelial growth factor therapy. The desired results of this activity are to help retina specialists provide better outcomes for their patients with polypoidal choroidal vasculopathy.

TARGET AUDIENCE

This educational activity is intended for retina specialists, including fellows.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Review the prevalence and pathobiology of polypoidal choroidal vasculopathy
- Illustrate how different imaging modalities can be used to diagnose polypoidal choroidal vasculopathy
- Demonstrate how photodynamic therapy can be incorporated appropriately into the management of patients with polypoidal choroidal vasculopathy, especially those with anti–vascular endothelial growth factor treatment-resistant disease

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MANAGING ANTI–VEGF-RESISTANT NEOVASCULAR AMD: IS IT POLYPOIDAL CHOROIDAL VASCULOPATHY?

Introduction

Polypoidal choroidal vasculopathy (PCV) is a form of choroidal neovascularization (CNV) that is characterized by the presence of aneurysmal, polyp-shaped structures beneath the retinal pigment epithelium (RPE), frequently in association with a variably organized branching vascular network (BVN). Originally described as a distinct clinical entity by Yannuzzi in 1982,[1,2] PCV is now increasingly recognized as an anatomic subtype of neovascular age-related macular degeneration (nAMD). Timely recognition and accurate diagnosis of PCV has important prognostic and therapeutic implications. Treatment with intravitreal anti–vascular endothelial growth factor (VEGF) drugs has greatly improved visual outcomes for patients with PCV. However, PCV is associated with a high rate of resistance to anti-VEGF treatment, which increases the risk for long-term vision loss.[3] This review provides expert perspectives on the diagnosis and treatment of PCV, including the role of verteporfin photodynamic therapy (PDT), particularly in patients with anti–VEGF treatment-resistant nAMD.

—Scott W. Cousins, MD

Case 1. Role of Indocyanine Green Angiography in the Diagnosis of Polypoidal Choroidal Vasculopathy

A 69-year-old white female with age-related macular degeneration presented with sub-RPE hemorrhage, serous pigment epithelial detachment (PED), and subretinal fluid seen by optical coherence tomography (OCT) ***(Figure 1)****. Indocyanine green angiography (ICGA) showed a cluster of polyps arising from a feeder vessel.*

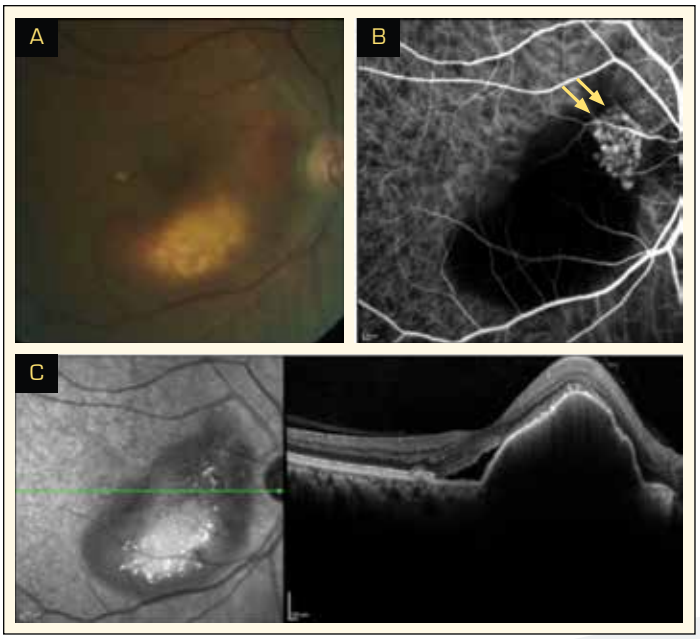

Figure 1. Sub–retinal pigment epithelium hemorrhage on examination (A), with serous pigment epithelial detachment and subretinal fluid seen by optical coherence tomography (C). Indocyanine green angiography (B) demonstrated a cluster of polyps arising from a feeder vessel (yellow arrows), superonasal to the pigment epithelial detachment and foveal region.

Images courtesy of Priyatham S. Mettu, MD

Dr Cousins: The clinical and OCT findings in this patient are characteristic of PCV, but are they adequate for establishing a diagnosis?

Dr Kokame: In his initial report on PCV, Yannuzzi described a series of patients with serosanguinous bleeding in the macula, PED, and peculiar orange subretinal lesions.[1,2] These features became widely recognized as "textbook" clinical characteristics of PCV, but they are inadequate for establishing the diagnosis because they are also typical of nAMD. Diagnosing PCV requires more than fundus examination/photography, OCT, and fluorescein angiography (FA). Scanning laser ophthalmoscope-based, high-speed ICGA is the gold-standard technology for diagnosing PCV.[4]

Dr Mettu: I agree that ICGA is vital for diagnosing PCV. ICGA reveals additional characteristic findings, including aneurysmal vascular dilatations or polypoidal lesions, often with a BVN. In contrast to FA, which depicts CNV leakage, ICGA reveals the structure and morphology of CNV. High-speed ICGA videoangiography depicts dynamic filling of CNV lesions, allowing differentiation of low- and high-flow neovascular structures. Use of the ICGA video, along with midframes (~3 minutes) and late frames (~6 minutes), allows us to visualize filling of the entire PCV complex.

Dr Waheed: Although the other imaging tests are less sensitive than ICGA, they often provide clues that can point to PCV. For example, a pointed or peaked PED is often seen on OCT, and a "double hump" PED configuration, as depicted in this case, is highly characteristic of PCV.[5] Increased choroidal thickness, which can also be seen on OCT with PCV, is neither sensitive nor specific for PCV. No single FA leakage pattern is specific for PCV, although PCV is one of several ICGA anatomic subtypes associated with occult or minimally classic leakage patterns.

Dr Cousins: How would you describe the pathobiology of PCV?

Dr Waheed: PCV is typically characterized by a type I subretinal neovascular membrane, which is located below the RPE, growing either between the RPE and Bruch membrane or within the Bruch membrane.[6,7] Histopathologic studies have demonstrated that polyp structures represent large, thin-walled, cavernous vascular channels, with accompanying choroidal neovascularization within the Bruch membrane.[8] Polyps can arise as terminal dilatations from a feeder artery with BVN or can be found in association with a poorly organized neovascular structure with interconnected vascular channels. Clinically, polyp lesions pose a significant risk of vision loss for affected patients because they are highly exudative and very prone to hemorrhage.[9]

Dr Mettu: The frequent association with a BVN suggests a possible pathobiologic link between PCV and the branching arteriolarized vascular complex subtype of nAMD. Because macrophages are thought to drive the development of arteriolarized neovessels, inflammation might be involved in the pathogenesis of PCV.

Dr Cousins: In the United States, what is the prevalence of PCV in patients with nAMD?

Dr Mettu: Using ICGA in the PERSIST study,[10] we found PCV in approximately 22% of patients with newly diagnosed nAMD in our practice. Our practice comprises mostly white patients (95%). In some patients with nAMD who were not initially diagnosed with PCV, we have also observed that lesions evolve to include polyp structures. In our experience, PCV is particularly common in patients requiring ongoing monthly anti-VEGF injections and in those with anti–VEGF-resistant disease.[10]

Dr Waheed: In the United States, PCV was thought to be rare in whites and more common in African Americans. I think we are beginning to appreciate, however, that PCV is significantly underdiagnosed, likely because retina specialists are reluctant to obtain ICGA routinely.

Dr Kokame: Recent studies of white-predominant populations from Brazil, Hawaii, and Switzerland using ICGA reported PCV prevalence rates ranging from 21.5% to 31.1%.[11–13] Given the risk of vision loss for untreated PCV, the high rate of persistent disease activity associated with PCV, and the potential clinical efficacy of anti-VEGF therapy and combination therapy incorporating verteporfin PDT,[9-12] it is now more important than ever to make the diagnosis of PCV.

Dr Cousins: What is the prevalence of PCV in Asian patients with nAMD?

Dr Kokame: Reported PCV prevalence rates in Asian patients with nAMD range from 22.3% to 61.6% in Chinese, Singaporean, and Southeast Asian populations to more than 50% in Japan.[14]

Dr Cousins: Is PCV different in whites than in Asians?

Dr Kokame: From a pathobiologic standpoint, it is unclear. A recent study from Lee and colleagues, however, found that patients with nAMD in Singapore and those in the United States had similar genetic profiles,[15,16] suggesting that there is not likely to be a genetic difference between white and, at least certain, Asian populations. From a pragmatic and clinical standpoint, rates of anti-VEGF resistance and the efficacy of adjunctive verteporfin PDT appear to be similar across white and Asian populations.

Dr Cousins: Dr Kokame, you have mentioned verteporfin PDT as a treatment option (see Sidebar: Clinical Applications of Photodynamic Therapy in Patients With Polypoidal Choroidal Vasculopathy). Please discuss briefly the historical context of PDT, its mechanism of action, and its potential efficacy for PCV.

Dr Kokame: Verteporfin PDT was initially introduced 18 years ago as a monotherapy for nAMD of the predominantly classic FA leakage subtype on the basis of the TAP (Treatment of AMD With Photodynamic Therapy) study.[17,18] Verteporfin is injected intravenously into the systemic circulation. As it circulates through the retinal vasculature, the verteporfin

molecule is activated by directing a nonthermal red laser of 693-nm wavelength at the macular lesion, with treatment customized by spot size, fluence energy level, and treatment duration. Once photoactivated, verteporfin triggers production of reactive oxygen species that cause damage confined to the vascular endothelium of the lesion targeted by the laser. This locally induced phototoxicity causes platelet aggregation and thrombosis, and ultimately targets vaso-occlusion of the CNV, which remains inactive until there is reperfusion.

In the case of PCV, targeted application of PDT to the polypoidal lesion, which includes the BVN and polyp structures, can be highly effective for achievement of polyp regression. The EVEREST study has previously demonstrated that PDT alone or in combination with ranibizumab was far more effective than ranibizumab monotherapy in effecting polyp regression.[19]

Dr Cousins: Dr Mettu, please explain the treatment and outcomes of the patient in this case.

Dr Mettu: This patient received 3 consecutive monthly injections with aflibercept, but had persistent PED and subretinal fluid in spite of treatment. Addition of adjunctive PDT applied to the PCV with BVN lesion promoted closure of the PCV lesion and resolution of disease activity.

Case 2. Neovascular Age-Related Macular Degeneration: Minimally Classic Subfoveal Choroidal Neovascularization With Polypoidal Choroidal Vasculopathy Seen by Indocyanine Green Angiography

*A 64-year-old white male presented with new-onset nAMD, with a minimally classic CNV leakage pattern seen by FA and a pointed spongiform PED and subretinal fluid seen by OCT **(Figure 2)**. ICGA revealed several large polyps arising from a BVN.*

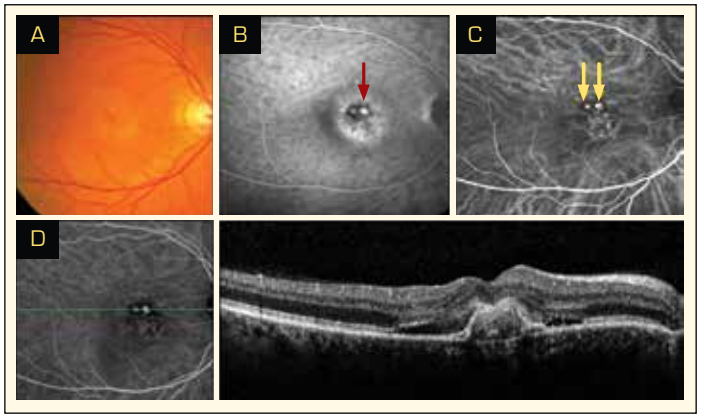

Figure 2. A minimally classic lesion (A) seen by fluorescein angiography (B; red arrow corresponds to pointed pigment epithelial detachment). Indocyanine green angiography (C) demonstrated several large polyps (yellow arrows) fed by a branching vascular complex. Subretinal fluid and pointed pigment epithelial detachment was seen by optical coherence tomography (D).

Images courtesy of Scott W. Cousins, MD

Dr Cousins: This patient has PCV in the setting of nAMD. Do you routinely order ICGA when evaluating patients with nAMD?

Dr Waheed: I tend to use OCT angiography (OCTA) **(see Sidebar: Next-Generation Imaging Technologies for the Diagnosis of Polypoidal Choroidal Vasculopathy)** as my primary angiography tool; in most cases, it gives me the information I need. I order ICGA if I suspect PCV but do not see it with OCT/OCTA or in the setting of persistent activity after starting anti-VEGF therapy for nAMD.

Dr Kokame: Given the high prevalence of PCV in my practice, which is composed of Asians and whites, I tend to obtain ICGA in most patients.

Dr Mettu: I follow a similar approach. I find ICGA helps to identify patients with PCV who might benefit from the addition of PDT to anti-VEGF therapy and to guide patient expectations for response to treatment and long-term prognosis.

Dr Cousins: Dr Mettu mentioned adjunctive PDT. What is its efficacy for treating PCV?

Dr Kokame: As mentioned earlier, targeted application of PDT to the polypoidal lesion can be effective for achieving polyp regression, and the EVEREST study demonstrated its efficacy.[19] In addition, there is a higher risk of relative resistance to antiangiogenic injections in eyes with PCV.

Dr Cousins: How would you treat the patient in this case, who has PCV in the setting of nAMD?

Dr Waheed: Because he has active CNV, I would initiate anti-VEGF therapy with a "loading dose" of 3 consecutive monthly injections and then assess the response. I tend to treat patients with PCV more aggressively with monthly injections and am slower to begin a treat-and-extend regimen.

Dr Mettu: I also would start anti-VEGF therapy. I might add PDT, however, if I see worsening during the loading-dose phase. I certainly would consider PDT if there is persistent or worsening disease activity after anti-VEGF loading.

Dr Kokame: Interestingly, there is new compelling evidence from EVEREST II that supports considering the combination of anti-VEGF therapy and PDT as a primary treatment option for patients with nAMD and PCV.[20] Conducted in centers across Asia, EVEREST II was a double-masked trial randomizing 322 treatment-naïve patients to either ranibizumab monotherapy (n = 154) or ranibizumab and verteporfin PDT (n = 168). At 12 months, the combination regimen was not only noninferior to ranibizumab monotherapy for improvement in best-corrected visual acuity (BCVA), but actually superior in analyses of functional improvement (8.3 vs 5.1 ETDRS letters, respectively; mean difference, 3.2 letters) and complete polyp regression (69.3% vs 34.7%, respectively, $P < .001$). Furthermore, adding PDT minimized the ranibizumab injection burden (median of 4.0 vs 7.0, respectively).

My clinical experience mirrors the data from EVEREST II in that I find PDT can be very helpful in achieving early polyp regression and reducing anti-VEGF treatment burden in eyes with PCV and nAMD. Nevertheless, I start with anti-VEGF therapy alone if visual acuity is relatively good because, historically, there is

a 1% to 2% risk of sudden vision loss with PDT.[18] If BCVA is 20/60 or worse, then I often discuss with patients the possibility of adding PDT initially or earlier in the course of anti-VEGF treatment.

Dr Cousins: How was the patient in this case treated?

Dr. Waheed: The patient received a loading dose with 3 consecutive monthly injections of ranibizumab. Following this, he had quiescent disease, but had recurrence of leakage on extension of the treatment interval; adjunctive PDT was added to achieve disease control.

Case 3. Neovascular Age-Related Macular Degeneration With Persistent Disease Activity

A 75-year-old white female with nAMD is seen on referral because of persistent disease activity after 6 monthly bevacizumab injections. Her BCVA is 20/80. An occult CNV leakage pattern is seen on FA. OCT reveals a spongiform PED, subretinal fluid, and subretinal hyperreflective material, and ICGA demonstrates polyps arising from a BVN ***(Figure 3)****.*

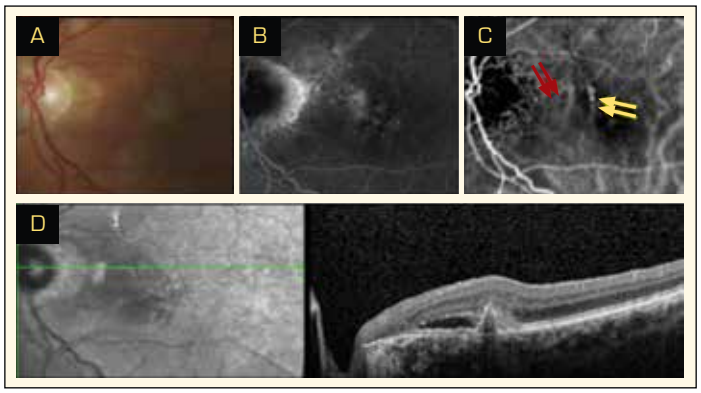

Figure 3. Fundus photographs from a patient with active neovascular age-related macular degeneration persisting after 6 monthly bevacizumab injections (A). Active leakage seen by fluorescein angiography (B) as well as peaked spongiform pigment epithelial detachment, subretinal fluid, and subretinal hyperreflective material seen by optical coherence tomography (D) despite 6 monthly bevacizumab treatments. Indocyanine green angiography (C) revealed a branching vascular network (red arrows) with polyps (yellow arrows).

Images courtesy of Priyatham S. Mettu, MD

Dr Cousins: How do you define anti–VEGF-resistant nAMD and persistent disease?

Dr Mettu: An eye would be considered to be anti-VEGF resistant if quiescence—defined as resolution of leakage without growth in lesion size—was not achieved after a sustained course of monthly anti-VEGF therapy—at a minimum, a loading dose of 3 monthly treatments. An incomplete response to anti-VEGF therapy identifies persistent disease. On OCT, we might see intraretinal fluid, subretinal fluid, and a serous PED. Often, there is prominent spongiform intermediate reflectivity PED, suggesting the presence of a perfused vessel. Fluorescein angiography might reveal persistent leakage and lesion growth. On clinical examination, we can often appreciate both progressive fibrosis and either a persistent or breakthrough hemorrhage while on treatment.

Dr Cousins: How frequently is persistent disease encountered? Does it matter when PCV is involved?

Dr Waheed: In CATT (Comparison of Age-Related Macular Degeneration Treatments Trials), which enrolled patients with active CNV due to AMD and did not investigate patients with PCV, persistent fluid on OCT was seen in 53.2% of patients receiving monthly ranibizumab, 70.9% of patients receiving monthly bevacizumab, 71.2% of patients receiving ranibizumab as needed, and 79.0% of patients receiving bevacizumab as needed.[21] By month 24, increased lesion size was also seen, most often in the bevacizumab as-needed group.[22]

Dr Mettu: OCT does not always reveal activity within the choroid, so there are frequently cases of persistent disease activity that might not be evident on OCT, but will be detected on FA, either in the form of persistent leakage or lesion growth. Both of these issues can affect long-term vision and disease control. Presence of PCV, in particular, can increase the risk of associated hemorrhage, highlighting the need for early diagnosis by ICGA. Retina specialists might not be doing enough angiograms to observe these phenomena.

Dr Waheed: The PIER study demonstrated that the level of disease activity at 3 months was predictive of visual acuity outcomes at 1 year.[23] The study suggested that FA can help identify patients who can sustain visual acuity gains with less frequent therapy. Those with a dry macula seen by FA at 3 months had better 1-year vision than those with a wet macula at 3 months. That said, I treat according to OCT results because the overwhelming majority of clinical trials have used OCT, not FA, to monitor disease progression. Additionally, OCTA studies have shown that patients might continue to do well visually despite enlarging CNVs so long as these CNVs are not accumulating fluid.[24] I do not routinely treat a nearly dry macula with continued aggressive anti-VEGF therapy; once the macula is dry, I consider extending the interval between treatments. It is important to make sure we are treating the patient and not the test. If the patient is doing well, I take that into account.

Dr Cousins: How would you approach treatment for this patient?

Dr Waheed: Because her disease has been resistant to bevacizumab, I would first consider switching this patient to either aflibercept or ranibizumab to see if her response to treatment improves. In my experience, and especially in patients with PCV, there is a subset of patients that responds better to aflibercept than to bevacizumab, although I do have to note that there is a paucity of data to support switching treatment. Very few well-designed studies have shown that switching makes a difference in response.

Dr Mettu: I, too, would switch drugs if the patient's insurance coverage allowed it, but I would inform the patient that there is a high likelihood that we might need to add PDT to achieve disease quiescence.

Dr Kokame: I would switch drugs as well, but given that her visual acuity is worse than 20/60, I would also proceed to combination therapy with PDT.

Dr Cousins: Is there any evidence that PCV might specifically respond better to one anti-VEGF drug than to another?

Dr Kokame: There are no studies that directly compare anti-VEGF agents specifically for the treatment of PCV. Currently, there are data to support the efficacy of anti-VEGF monotherapy for the treatment of PCV. For example, in the 6-month EPIC (Prospective Clinical Trial of Intravitreal Aflibercept Treatment for Polypoidal Choroidal Vasculopathy With Hemorrhage or Exudation) study, we found that aflibercept monotherapy was associated with stabilized vision, resolution of fluid and hemorrhage, and polyp regression in approximately 70% of 21 patients.[25] However, some patients who switched from the 2.0-mg ranibizumab study (PEARL II)[7] to the 0.5-mg aflibercept study (EPIC) showed a better response anecdotally. Also, aflibercept tends to be the preferred treatment choice for PCV in Asia. In the PLANET (Aflibercept in Polypoidal Choroidal Vasculopathy) study, the visual outcome with aflibercept monotherapy was noninferior to aflibercept and PDT over 12 months of treatment,[26] although so few eyes received PDT in this study that one could not make any conclusions about its role.

Dr Mettu: These data mirror our findings in the PERSIST study, in which the rate of persistent disease activity was lower in patients receiving loading-dose treatment with aflibercept than in a historical comparator group receiving bevacizumab.[10]

Dr Kokame: Although PCV might respond better to aflibercept, it is important to remember that the efficacy of combination anti-VEGF therapy plus verteporfin PDT is well established. As discussed earlier, data from EVEREST and EVEREST II support the use of combination therapy, particularly for achieving polyp regression.[19,20] Findings of a recent meta-analysis showing significantly greater BCVA improvement and significantly greater polyp regression with combination therapy than with anti-VEGF monotherapy provide further support for combination therapy.[27]

Case (Continued)

Photodynamic therapy was applied to the PCV and BVN lesion in combination with intravitreal triamcinolone and aflibercept. At 1 month post PDT, there was partial vaso-occlusion and resolution of disease activity ***(Figure 4)****.*

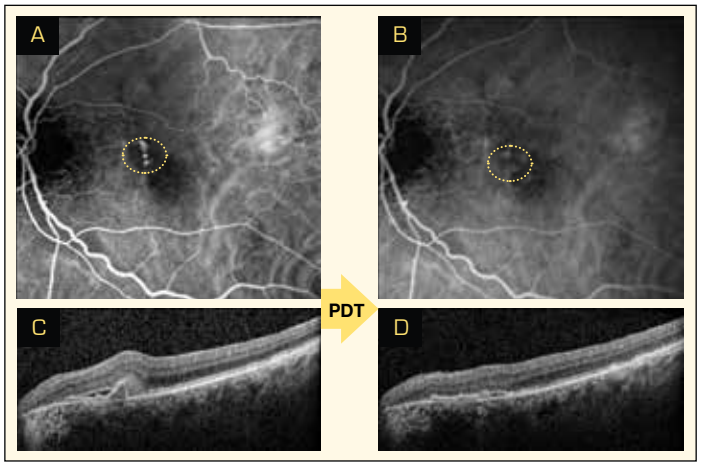

Figure 4. Following photodynamic therapy (PDT) targeted to the lesion (A and C), vaso-occlusion of the branching vascular network and polyps (B) resulted in collapse of the pigment epithelial detachment as well as resolution of subretinal fluid and subretinal hyperreflective material (D).

Images courtesy of Priyatham S. Mettu, MD

Clinical Applications of Photodynamic Therapy in Patients With Polypoidal Choroidal Vasculopathy

Dr Cousins: In the case discussions, we address the role of photodynamic therapy (PDT) in the treatment of patients with polypoidal choroidal vasculopathy. Dr Mettu, how do you generally apply PDT in your patients with polypoidal choroidal vasculopathy?

Dr Mettu: Traditionally, application of PDT was guided by fluorescein angiography (FA), wherein the spot size was adjusted to encompass the entire area of classic leakage by FA. Although this approach achieves vaso-occlusion in a high percentage of cases, it also carries at least a 1% to 2% risk of sudden vision loss secondary to occlusion of normal choroidal vasculature.[1] Indocyanine green angiography (ICGA) is vital for modern application of PDT because it affords visualization of the discrete neovascular structure and permits narrowing of the spot size to target the choroidal neovascularization, limiting effects on normal choroid.

Dr Cousins: Do you treat the whole lesion or target the polyps?

Dr Kokame: We measure the entirety of the lesion according to ICGA, not according to FA. We then include the branching vascular network (BVN) and polyps, and add only 300 µm to the greatest linear diameter to determine the treatment spot size. On the same day, we give intravitreal anti–vascular endothelial growth factor (VEGF) and dexamethasone injections. The treatment spot size on ICGA is much smaller than the spot size traditionally used in the past according to FA, which added 1000 µm to the greatest linear diameter around the area of leakage.

Dr Mettu: We take a slightly different approach. We target the base of the feeder arteriole of the BVN and then apply a second treatment to the polyps themselves. It is helpful to focus on the early images or video of the ICGA because this is typically when the high-flow BVN is best visualized, although late- (~3 minutes) and very late– (~6 minutes) phase images might be necessary to visualize low-flow polyps that fill slowly.

In addition, we inject low-dose intravitreal triamcinolone (0.25 mg) to limit any proinflammatory effects of PDT. Although we occasionally do same-day intravitreal anti-VEGF therapy, we strive to give the anti-VEGF agent 1 week prior to PDT because increased levels of VEGF and inflammatory mediators might drive exudation post PDT.

Dr Cousins: What is the significance of pulsatile polyps? Do you modify your treatment plan to address them?

Dr Waheed: Pulsatile polyps might be evidence of increased perfusion pressure. If the patient has elevated blood pressure in the setting of pulsatile polyps, I might defer PDT until blood pressure is better controlled in order to reduce the risk of submacular hemorrhage following PDT.

Dr Cousins: What factors influence your PDT treatment parameters?

Dr Kokame: I use visual acuity to guide my approach. I typically use standard full fluence, 50 J/m^2, if visual acuity is 20/60 or worse, but otherwise I use half-fluence, 25 J/m^2. The RADICAL (Reduced Fluence Visudyne-Anti-VEGF-Dexamethasone in

Combination for AMD Lesions) study demonstrated that half-fluence PDT can be effective for treating neovascular age-related macular degeneration in the setting of PDT and anti-VEGF combination therapy.[2] In EVEREST II, however, standard full fluence was used and was not associated with any cases of sudden vision loss.[3]

Dr Mettu: I tend to use full fluence for all my PDT treatments, but I vary the treatment duration. For juxtafoveal and extrafoveal lesions, I perform full duration (~83 seconds); for subfoveal lesions, I start with half duration (~42 seconds) and consider retreating at full duration if the response is suboptimal.

Dr Cousins: When do you repeat imaging after PDT?

Dr Kokame: I typically get a standard optical coherence tomography (OCT) and ICGA 4 to 6 weeks after PDT to see if the lesion has shut down. If I see residual subretinal or intraretinal fluid, I repeat the anti-VEGF injection.

Dr Mettu: I perform ICGA at 4 weeks post PDT because it is useful to know if vaso-occlusion was achieved, and if not, whether or not the flow rate through the lesion decreased. I find that cases with residual subretinal or intraretinal fluid or residual serous pigment epithelial detachment (PED) are often more responsive to anti-VEGF treatment following PDT, probably because there is diminished flow or decreased perfusion of the choroidal neovascularization lesion.

Dr Waheed: I do not routinely obtain ICGA following PDT because I am not convinced that it will change my management. I do assess the lesion posttreatment by looking at the size of the PED and the hyperreflective material representing neovascular tissue under the PED.

Dr Cousins: What is the typical durability of PDT?

Dr Mettu: Durability of PDT varies and can be difficult to predict, but I think it is important to keep a few points in mind. First, although disease recurrence is not infrequent, PDT can be repeated safely multiple times to try to reattain a quiescent disease state.[4] In such cases, I tend to wait at least 3 months between treatments. Second, adjunctive PDT does not typically eliminate the need for continued anti-VEGF therapy for long-term disease control. For this reason, I maintain anti-VEGF treatment on a treat-and-extend strategy to maximize the likelihood of sustained quiescence.

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Case 4. Persistent Disease Activity Associated With Serous Pigment Epithelial Detachment

*A 79-year-old white female with nAMD presented with a typical serous PED **(Figure 5).** The FA revealed some hyperfluorescence at the 11 o'clock position that was determined with ICGA to be PCV with a BVN. The patient underwent a loading dose of anti-VEGF therapy, without resolution of the PED.*

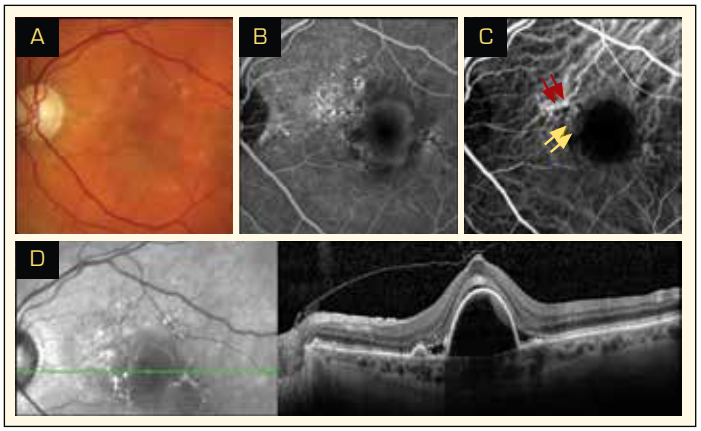

Figure 5. Fluorescein angiography (A) revealed a serous pigment epithelial detachment with associated occult leakage pattern at 11 o'clock (B). Indocyanine green angiography (C) revealed a branching vascular network (red arrows) with polyps (yellow arrows). There were serous pigment epithelial detachment and subretinal fluid on optical coherence tomography (D).

Images courtesy of Scott W. Cousins, MD

Dr Cousins: Dr Mettu, what are the different kinds of PED? Are they a manifestation of nAMD?

Dr Mettu: Several different types of PED can be associated with nAMD, including serous, spongiform, and hemorrhagic PEDs; an additional type, drusenoid, is a manifestation of dry age-related macular degeneration. Serous PEDs, in particular, have represented both a diagnostic and treatment challenge because there has always been a question of whether or not they are truly neovascular. This issue has become more relevant in the anti-VEGF therapy era. Serous PEDs frequently do not respond well to anti-VEGF therapy because they are frequently associated with complex lesions such as PCV, as in this case, or with arteriolarized vascular complexes.[28]

Dr Cousins: Arteriolarized vascular complexes and PCV cannot always be appreciated on FA or OCT. Do you routinely obtain ICGA upon presentation for a patient with a serous PED?

Dr Mettu: I do so that I can determine the presence and location of the associated neovascular lesion.

Dr Kokame: I might not get an ICGA when there is an isolated serous PED, but I would definitely get one if I suspect there is any serous detachment, macular edema, or subretinal fluid.

Dr Waheed: It can sometimes be difficult to differentiate between pooling and leakage on FA. In such cases, I find ICGA or ICGA in combination with OCTA to be helpful.

Dr Cousins: How do you treat a patient with a serous PED and PCV?

Dr Waheed: I prefer localized PDT applied to the area of the vascular lesion, not to the whole PED.

Dr Kokame: I agree. My agreement is based on the concept that the PED is arising from abnormal fluid exudation from the adjacent neovascular lesion into the Bruch membrane. Successful vaso-occlusion of the PCV lesion should promote collapse of the serous PED.

Case (Continued)

The patient was treated with PDT to the PCV and BVN lesion, leading to collapse of the serous PED and resolution of disease activity ***(Figure 6)****.*

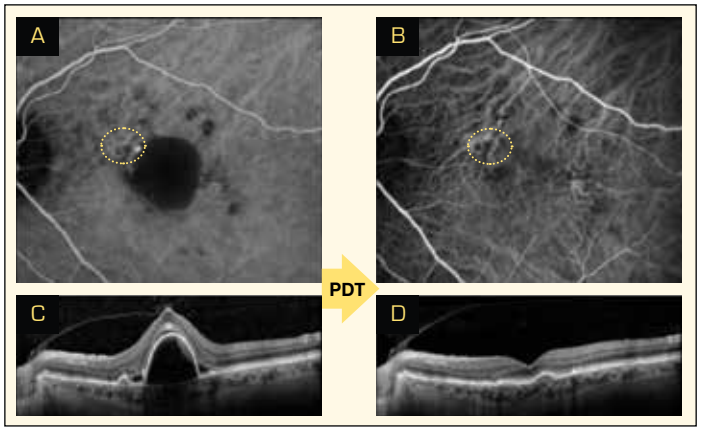

Figure 6. Images from indocyanine green angiography (A and B) and spectral-domain optical coherence tomography (C and D). Following photodynamic therapy (PDT) targeted to the lesion (A and C), vaso-occlusion of the branching vascular network and polyps (B) resulted in collapse of the pigment epithelial detachment as well as resolution of subretinal fluid (D).

Images courtesy of Scott W. Cousins, MD

Dr Cousins: How would you manage this patient post PDT?

Dr Kokame: I often base my decision on the appearance of the fundus and the OCT because, in my experience, the anatomic findings on ICGA often do not correlate with the fundus appearance or with the patient's visual status. If there is residual fluid or leakage, I give anti-VEGF therapy, but if the PED regressed and there is no fluid or leakage, I often observe the patient and give anti-VEGF treatment as needed for disease reactivation. If there are new polyps, reperfusion of existing polyps, new bleeding, or recurrence/worsening of PED, then I repeat the ICGA and consider repeat PDT.

Case (Continued)

The patient was maintained on aflibercept every 6 weeks. At 4 months post PDT, the serous PED recurred in association with reperfusion of the PCV lesion.

Dr Cousins: How common is disease recurrence following PDT? Can PDT be repeated?

Dr Waheed: In the pivotal studies for PDT[17,18] and in subsequent real-world clinical practice, recurrence of disease was quite common following traditional FA-guided PDT. I think such recurrences are not infrequent—even with a targeted approach enabled by ICGA guidance—because the CNV represents a chronic disease process, in which reperfusion of the original lesion or growth of new neovascular structures from the original lesion leads to recurrence.

Dr Kokame: In EVEREST II, patients in the PDT and ranibizumab group could receive repeat PDT for recurrent disease and/or worsened vision in association with an active PCV lesion detected by ICGA/FA if at least 3 months had elapsed since the last PDT treatment.[20] It is interesting to note that using this criterion for retreatment in patients who were also receiving as-needed anti-VEGF treatment, the mean number of PDT treatments over 12 months was 1.5, with 61.0% of patients in the combination treatment group needing only the initial PDT and 87.7% of patients requiring ≤ 2 PDT treatments. These data provide strong evidence that even in cases in which disease recurs following PDT, it can be successfully managed with appropriate anti-VEGF treatment.

Next-Generation Imaging Technologies for the Diagnosis of Polypoidal Choroidal Vasculopathy

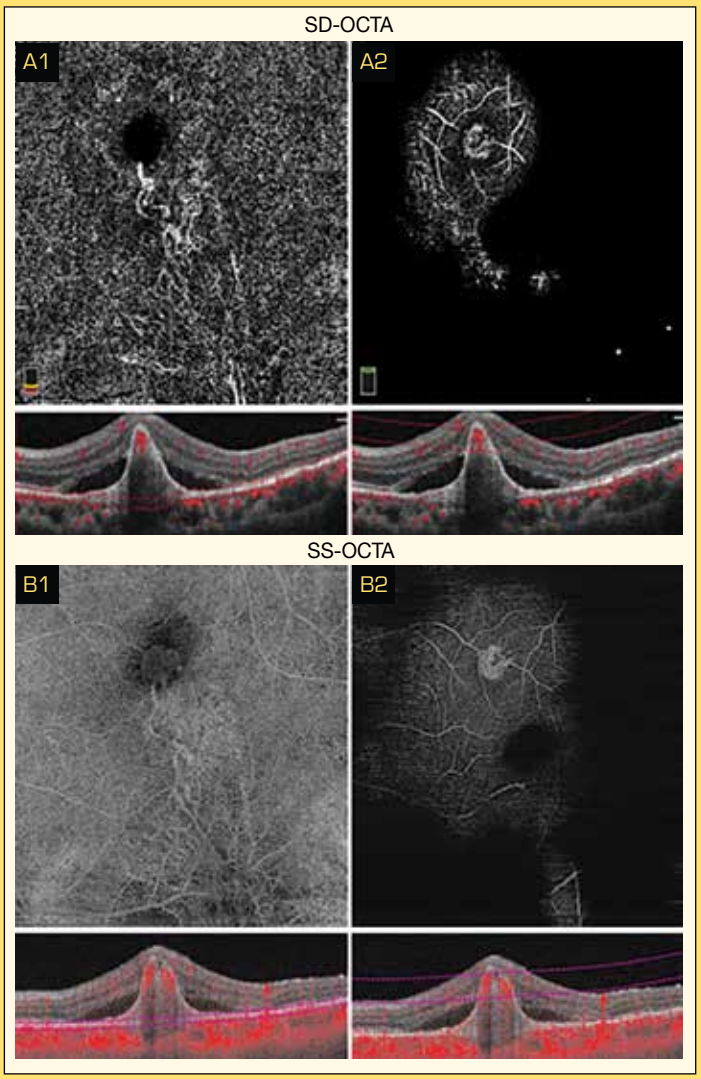

Figure 1. Spectral-domain optical coherence tomography angiography (SD-OCTA) with segmentation along the base of the pigment epithelial detachment (PED)/Bruch membrane demonstrates the branching vascular network as an irregular vascular structure (A1). Segmentation along the peak of the PED demonstrates a round vascular structure resembling a polyp (A2). Swept-source optical coherence tomography angiography (SS-OCTA) with segmentation along the base of the PED/Bruch membrane more clearly demonstrates the full extent of the branching vascular network, with structures resembling branching arterioles, draining veins, and a faint round structure suggesting a polyp (B1). Segmentation along the peak of the PED more clearly demonstrates what appears to be a polyp (B2).

Images courtesy of Nadia Khalida Waheed, MD

Dr Cousins: Optical coherence tomography angiography (OCTA) is a noninvasive approach for imaging the microvasculature of the retina and choroid. There are 2 spectral-domain (SD)-OCTA systems and 1 swept-source (SS)-OCTA platform commercially available in the United States. How do the SD-OCTA platforms perform for detecting polyps?

Dr Waheed: As the images in **Figure 1** illustrate, OCTA can detect polyps, but its efficacy depends on the segmentation of the B-scans and on the relative flow rate. One has to pay careful attention when viewing through the en face layers of the OCTA that the segmentation is correct and not artifactual. I find that it is most useful to look at the B-scans with the flow overlay because these are segmentation independent. Looking carefully for flow at the apex of the pigment epithelial detachment (PED), you might be able to detect polyps that are harder to make out in the en face images. Overall, SD-OCTA might not be able to detect some polyps because of poor penetrance with past PEDs as well as its limitations in detecting slower flow speeds.

Dr Kokame: In our studies, we found that OCTA produced some compelling images of polyps and the associated branching vascular network (BVN). However, OCTA is not ready to replace indocyanine green angiography as the gold standard for diagnosing polypoidal choroidal vasculopathy (PCV) because its sensitivity and specificity have been shown to be only 43.9% and 87.1%, respectively.[1]

Dr Cousins: Will SS-OCTA provide greater sensitivity for detecting polyps?

Dr Waheed: Better depth penetrance incorporated with the longer wavelengths of SS-OCTA units, along with improved algorithms to assess differential flow over time, will improve detection of polyps as OCTA technologies continue to evolve. The SS-OCTA images nicely illustrate its improved resolution and imaging relative to SD-OCTA **(Figure 1)**.

Dr Cousins: Figure 2 shows indocyanine green angiography, SD-OCTA, optical coherence tomography (OCT) B-scan, and structural en face OCT images from eyes with PCV. Dr Kokame, please tell us more about imaging with structural en face OCT scans in such cases.

Dr Kokame: Often, the structural en face OCT scan is effective in outlining the extent of the BVN, which is apparent as elevated, slightly thickened "geographic" patterns. Polyps are evident as small, highly reflective circles adjacent to or within the presumed BVN. Clear polyp structures are frequently difficult to visualize, but there are clues when looking at OCT B-scans, along with the structural scan map. In our study, the sensitivity and specificity of structural en face OCT for detecting polyps were 30% and 85.7%, respectively, and improved to 43.9% and 87.1%, respectively, after combining it with OCTA.[1]

Dr Cousins: Do you incorporate OCTA and structural en face OCT scans in clinical practice?

Dr Waheed: As a noninvasive test and because of its rapid acquisition, OCTA is a convenient and attractive addition to my imaging armamentarium. If it clearly shows the neovascular structures, I can avoid angiography with injectable dyes.

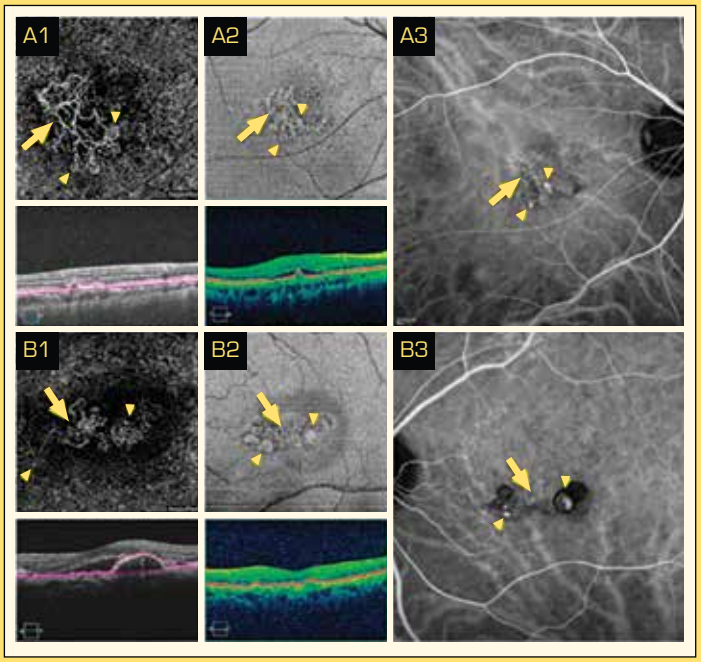

Figure 2. Images from a 72-year-old Korean male (A) and a 74-year-old Japanese male (B). Indocyanine green angiography (A3 and B3) and spectral-domain optical coherence tomography (OCT) angiography (A1 and B1) demonstrate the branching vascular network (yellow arrow), with subtle evidence of polyp structures (yellow arrowheads). Inverted U-shaped "peaked" retinal pigment epithelium elevation on the corresponding OCT B-scan is suggestive of polyps (A1). Structural en face OCT scans (A2 and B2) reveal the outlines of the branching vascular network, with irregular foci corresponding to peaked retinal pigment epithelium elevations on OCT B-scans, suggestive of accompanying polyps.

Images courtesy of Gregg T. Kokame, MD

Dr Kokame: I tend to get OCTA along with OCT on many—if not most—of my patients. I believe that comparing the findings of OCTA with those of other imaging modalities will allow us to learn more about the value of OCTA and its potential role.

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Take-Home Points

- ICGA is the gold-standard technology for diagnosing PCV and guiding application of PDT.
- A pointed or peaked PED or double hump PED configuration on OCT is highly characteristic of PCV
- Noninvasive imaging with OCTA shows promise, but more work is needed to define its role for diagnosing PCV
- Polyp lesions pose a significant risk of vision loss because they are highly exudative and prone to hemorrhage.
- PCV appears to be more common in white-predominant populations than previously appreciated.
- The prevalence rates of PCV reported in studies using ICGA for diagnosis range from approximately 20% to 30%
- Data from EVEREST II support considering the combination of anti-VEGF therapy and PDT as primary treatment for patients with nAMD and PCV.

- More studies are needed to determine if PCV responds differently to various anti-VEGF therapies.
- Visual acuity, presence of pulsatile polyps, and lesion location relative to the fovea might affect planning of PDT treatment for PCV.

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1. What is the gold standard imaging tool for diagnosing PCV?
   A. High-speed ICGA
   B. SD-OCTA
   C. SS-OCTA
   D. FA

2. Imaging findings characteristic of PCV include all the following, EXCEPT:
   A. Double hump PED on OCT
   B. Occult leakage pattern on ICGA
   C. Peaked PED on OCT
   D. Predominantly classic leakage pattern on ICGA

3. The pathogenesis of PCV is thought to involve:
   A. Insulin-like growth factor 1 resistance
   B. Inflammation
   C. Mineralocorticoid receptor stimulation
   D. Rho kinase activation

4. The mechanism of action of PDT with verteporfin in the treatment of nAMD includes:
   A. Photoactivation of verteporfin
   B. Nitric oxide liberation from tissues
   C. Focal vascular occlusion within the CNV lesion
   D. Both A and C

5. In the PERSIST study, what was the prevalence rate of PCV?
   A. 5% to 10%
   B. 10% to 15%
   C. 15% to 20%
   D. 20% to 25%

6. In EVEREST II, at the end of 12 months, adding verteporfin PDT to ranibizumab was associated with all the following, EXCEPT:
   A. Increase in mean BCVA gain
   B. Increase in the rate of sudden vision loss
   C. Increase in the rate of complete polyp regression
   D. Reduction in the median number of ranibizumab injections

7. Data from the EPIC, PLANET, and PERSIST studies show good outcomes for treating PCV with the anti-VEGF agent _____.
   A. Aflibercept
   B. Bevacizumab
   C. Ranibizumab
   D. All the above

8. In a patient with PCV and pulsatile polyps, the PDT treatment plan might be modified by:
   A. Deferring treatment until elevated blood pressure is controlled
   B. Using half-fluence PDT
   C. Using half-duration PDT
   D. Waiting 1 week after PDT before injecting anti-VEGF therapy

9. Which of the following types of PED can be associated with PCV?
   A. Drusenoid
   B. Hemorrhagic
   C. Serous
   D. Either B or C