Polypoidal choroidal vasculopathy in Canada

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Wai-Ching Lam, MD, FRCSC,*,† Netan Choudhry, MD, FRCSC,‡ David Wong, MD, FRCSC†

Polypoidal choroidal vasculopathy (PCV) is an exudative age-related macular degeneration (AMD) subtype found more frequently among Asians than Caucasians. If untreated, it may lead to severe vision loss. PCV appears to be frequently underdiagnosed in Canada, although misdiagnosis of PCV as AMD carries the risk of inadequate treatment and unsatisfactory clinical outcomes. Diagnosis can be made on the basis of multimodal imaging, including optical coherence tomography (OCT) and OCT angiography combined with colour fundus photography, or by other imaging techniques; the gold-standard indocyanine green angiography (ICGA) is not widely used in Canada. Treatment involves anti−vascular endothelial growth factor (anti-VEGF) agents (bevacizumab, ranibizumab, or aflibercept), alone or in combination with photodynamic therapy (PDT). Recent clinical trials have shown that ranibizumab in combination with PDT is superior to ranibizumab monotherapy (EVEREST II), and aflibercept monotherapy is as effective in patients meeting PDT rescue criteria as aflibercept combined with rescue PDT (PLANET). It appears that most Canadian PCV patients are treated with anti-VEGF monotherapy, with or without PDT.

La vasculopathie polypoïdale choroïdienne (VPC) est un sous-type de dégénérescence maculaire liée à l'âge (DMLA) exsudative qui touche plus fréquemment les Asiatiques que les Caucasiens. En l'absence de traitement, la VPC risque d'entraîner une importante perte de vision. L'affection semble souvent sous-diagnostiquée au Canada; de plus, si l'on fait l'erreur d'attribuer un diagnostic de DMLA à une VPC, on risque de proposer un traitement inapproprié qui donnera des résultats cliniques insatisfaisants. Le diagnostic peut reposer sur l'imagerie multimodale, notamment la tomographie en cohérence optique (OCT) et l'angiographie-OCT, associée à la photographie en couleur du fond d'úil ou à d'autres techniques d'imagerie. Par ailleurs, la technique d'imagerie de référence − l'angiographie au vert d'indocyanine − n'est pas utilisée à grande échelle au Canada. Le traitement consiste en l'administration d'un anti-VEGF (facteur de croissance endothélial vasculaire) comme le bevacizumab, le ranibizumab ou l'aflibercept, seul ou en association à la thérapie photodynamique (TPD). Selon des études cliniques récentes, le ranibizumab associé à la TPD donne de meilleurs résultats que le ranibizumab en monothérapie (EVEREST II); de même, l'aflibercept en monothérapie est aussi efficace chez les patients qui répondent aux critères de la TPD de sauvetage que l'aflibercept administré en association à la TPD de sauvetage (PLANET). Il semble que la plupart des patients canadiens présentant une VPC reçoivent un anti-VEGF en monothérapie, avec ou sans TPD.

Polypoidal choroidal vasculopathy (PCV) is a subtype of exudative age-related macular degeneration (AMD) defined as polypoidal subretinal vascular lesions associated with serous and hemorrhagic detachments of the retinal pigment epithelium (RPE). When this condition was first described, proposed names included "multiple recurrent retinal pigment epithelial detachments in black women"[1] and "posterior uveal bleeding syndrome"[2]; however, "idiopathic polypoidal choroidal vasculopathy"[3] subsequently changed to "polypoidal choroidal vasculopathy" and has become widely accepted.

If untreated, PCV often follows a relapsing-remitting course with recurrent serosanguinous detachments of the RPE and neurosensory retina. However, some patients may develop chronic atrophy and cystic degeneration of the fovea associated with severe vision loss, whereas others may experience central vision loss due to vitreous hemorrhage or disciform scarring.[4]

Among patients with exudative AMD, PCV tends to be more common in Asians (22%−55% of patients; Table 1) than in Caucasians (8%−25%): a meta-analysis in white patients found a pooled prevalence of 8.7% (1 in 11 patients).[6] These populations also present differently: In

Table 1—Proportion of neovascular age-related macular degeneration patients diagnosed with polypoidal choroidal vasculopathy in various populations

Population	Proportion of nAMD Patients Diagnosed with PCV, %
Americans[5]	7.8
Belgians[8]	12
Brazilians[9]	24.5
Chinese[10,11]	22.3−24.5
Danes[12]	8
French[13]	9
Greeks[14]	8.2
Italians[15]	9.8
Japanese[13,16−19]	23−54.7
Korean[20,21]	22.2−24.6
Taiwanese[22]	49
United Kingdom[23]	9.1

nAMD, neovascular age-related macular degeneration; PCV, polypoidal choroidal vasculopathy.

Asian populations, PCV tends to be male dominated, more frequently unilateral, and often located in the macular area, while among Caucasians, it tends to be female dominated and more frequently bilateral, with lesions occurring in both macular and peripapillary regions.[7]

Polypoidal choroidal vasculopathy appears to be frequently underdiagnosed in Canada, due partly to indocyanine green angiography (ICGA) not being performed routinely, and partly to PCV not being considered by ophthalmologists, particularly when managing Caucasian patients. This hypothesis is supported by the results of a recently published study that reviewed all patients diagnosed with new AMD at 3 Ontario hospitals over 6 years (2445 eyes) and found that PCV had been diagnosed in only 6.5% of Chinese-Canadian patients and 0.7% of Caucasian-Canadians—rates much lower than those reported in epidemiological studies.[24]

In this study, ICGA—considered the gold standard of PCV diagnosis—was used to verify the diagnosis of only 20% of the Chinese-Canadian patients and 8.8% of the Caucasian-Canadian patients whose eyes were labelled as having PCV. This suggests that limited access to ICGA, which is not funded by the government of Ontario, may contribute to underdiagnosis.

Unfortunately, misdiagnosis of PCV as AMD carries the risk of inadequate treatment and unsatisfactory clinical outcomes, because PCV responds differently to commonly used therapies.[25] First-line treatments for AMD are anti−vascular endothelial growth factors (anti-VEGFs), but anti-VEGF studies in PCV patients have found that one of the anti-VEGFs is more effective in combination with photodynamic therapy (PDT): EVEREST II showed that ranibizumab produced better outcomes when administered in combination with PDT at baseline than as monotherapy.[26] This underscores the importance of accurate diagnosis of this condition.

Etiology and Pathogenesis

One approach to elucidating the etiology of PCV has been research into the levels of intraocular inflammatory cytokines in PCV patients. A number of proteins have been found at higher levels in PCV patients' aqueous humour than in that of controls, including growth-related oncogene, macrophage-derived chemokine, and several interleukins and other proteins.[27,28] Elevated levels of interleukins 1α, 4, 5, 10, and 23 have been found to be significantly associated with exudative lesions on fundus fluorescein angiography (FFA), suggesting the involvement of inflammatory processes in PCV etiology.[28] Interestingly, PCV patients' plasma cytokine levels are not elevated, suggesting that PCV pathology is primarily driven by dysregulation of local immune factors in the eye.[27]

Investigations into the genetic basis of PCV and AMD have demonstrated substantial sharing of genetic risk variants for PCV and typical neovascular AMD (although PCV does show some different genetic association patterns).[29] A multifunctional serine protease, HTRA1, which is linked to AMD, has also been found to be associated with PCV: overexpression of human HTRA1 in mouse RPE showed that increased HTRA1 was sufficient to cause PCV in mice.[30] Other risk factors also overlap between the 2 conditions: cigarette smoking is significantly associated with both AMD and PCV, and in both conditions certain polymorphisms interact with smoking to increase the risk further.[31,32]

Given that PCV patients differ in their responses to treatment, it has been hypothesized that an individual's genetic profile could also affect therapeutic outcomes. A recent study examined the relationship between 10 single nucleotide polymorphisms (in AMD-relevant genes) and patient responses to anti-VEGF monotherapy.[33] In the case of one polymorphism (ARMS2 rs10490924), additional G alleles increased the likelihood of pigment epithelial detachment (PED) regression after treatment, suggesting that a PCV patient's genetic background may indeed influence his or her response to anti-VEGF treatment.

In addition, both VEGF (an angiogenesis stimulator) and pigment epithelium-derived factor (PEDF, a protein that inhibits angiogenesis) have been shown to exist at increased levels in tissues from eyes with PCV. One study showed that VEGF and PEDF were strongly expressed in the vascular endothelial cells and RPE cells of PCV specimens, suggesting that both proteins may modulate the formation of subfoveal fibrovascular membranes.[34] Another study found that both factors were increased in the aqueous humour of eyes with active PCV, although to much lower levels than in eyes with AMD, implying that these 2 clinical entities might involve different pathogenesis processes.[35]

Pachychoroid may also have a role. One observational study found 6 cases of active PCV with typical central serous chorioretinopathy (CSC)−like active leakage and thick choroid in the same eye.[36] The authors speculated that, in an eye with a hyperpermeable pachychoroid, inability of the RPE to handle fluid overload associated with choriocapillaris loss could result in exudative macular detachment and CSC due to ischemia and breakdown of the RPE barrier.

Associated stress could lead to micro-rips in the Bruch's membrane, which would be another step toward neovascularization formation; polyps developed by a long-standing type 1 choroidal neovascular membrane (or as a result of chronic choroidal venous hypertension) would then result in PCV.

Diagnosing PCV

Although PCV was once described as an abnormality of the inner choroidal vasculature, histology and OCT have shown that its hallmark branching vascular networks (BVNs) of vessels with terminal aneurysmal dilatations are actually found between the RPE and Bruch's membrane. In OCT, this location of lesions beneath Bruch's membrane is one of the diagnostic characteristics that differentiate PCV from exudative AMD.

The presentation of PCV can vary widely, which contributes to the difficulty in diagnosis. Significant blood and/or exudation are always present, but exudation can occur without hemorrhage, and subretinal or sub-RPE hemorrhage can occur with or without other exudative characteristics. Hemorrhagic PCV can involve massive intraocular hemorrhage, breakthrough vitreous hemorrhage, and/or spontaneous suprachoroidal hemorrhage. Exudative PCV may be accompanied by neurosensory retinal detachment, RPE detachment, or the presence of subretinal lipid. Quiescent PCV involves asymptomatic, orange-red subretinal polypoidal lesions with overlying RPE atrophy.

Typical features of PCV on OCT include lesions beneath Bruch's membrane, increased choroidal thickness, a peaked PED (particularly if there is material on the undersurface) with moderate hyper-reflectivity (Fig. 1), a notched PED, and the "pearls on a string" presentation (Fig. 2). An appearance of BVNs as 2 highly reflective lines (the "double-layer sign") is also diagnostic, and focal choroid excavation may also be visible. *En face* OCT is particularly useful for demonstrating an entire BVN with its polypoidal lesions.

The combination of OCT and colour fundus photography (showing hemorrhage, exudation, and/or the characteristic orange-red polypoidal lesions) can frequently identify PCV without the need for invasive imaging. One study found that the presence of 2 out of 3 signs (PED, the double-layer sign, and thumb-like polypoidal lesions) on OCT would distinguish PCV from typical neovascular AMD with a sensitivity of 89% and a specificity of 85%.[37] Another small study looked at spectral-domain OCT in patients with one or more PEDs and found that it had a sensitivity of 94.6% and a specificity of 92.9% in differentiating PEDs attributable to PCV or occult choroidal neovascularization.[38]

A literature review by a panel of retinal experts noted that OCT is an excellent adjuvant for the diagnosis of PCV, especially when ICGA is unavailable.[39] The experts recommended suspecting PCV if any of the following is seen on OCT: a thumb-like polypoidal lesion or sharp-peaked PED; a tomographic notch in the PED; a hyporeflective lumen surrounded by a hyper-reflective ring attached to the undersurface of the RPE; or the double-layer sign. Classical PCV features such as a tall-peaked PED, a notched PED, the double-layer sign, and thumb-like polypoidal lesions can differentiate PCV from AMD to a large extent.

Optical coherence tomography—angiography (OCT-A) has the benefits of OCT plus the ability to visualize blood vessels through the movement of erythrocytes without the need for dye injection. This makes BVNs easier to detect, although polypoidal lesions may be hard to identify because of the variable flow rate (Fig. 3). Some clinicians find the images difficult and time-consuming to review. In addition, OCT-A is currently unable to demonstrate leakage, and vessel maps can be affected by imaging artifacts and errors of segmentation. Finally, OCT-A may not produce an image for the full extent of a PCV lesion and therefore cannot replace ICGA for photodynamic therapy.[40] A study comparing the accuracy of OCT-A and ICGA found that OCT-A detected fewer polypoidal lesions but more BVNs than did ICGA.[41] Another study found that OCT-A detected fewer polypoidal lesions of type 1 PCV (polypoidal choroidal neovascularization) than of type 2 (typical PCV), and detected only half of those type 2 polypoidal lesions detected with ICGA.[42]

Fundus autofluorescence (FAF) photography can identify autofluorescence patterns that occur more commonly in eyes with PCV than in those with typical neovascular AMD (Fig. 4B). One study found that confluent hypoautofluorescence was visible in 80.4% of eyes with PCV but no eyes with neovascular AMD.[43] In another study, FAF detected 4 characteristic autofluorescent patterns at the corresponding retinal sites of polypoidal lesions detected by ICGA: confluent hypoautofluorescence with a hyperautofluorescent ring, hyperautofluorescence with a hypoautofluorescent ring, confluent hypoautofluorescence, and granular hypoautofluorescence.[44]

FAF may also have potential in evaluating the therapeutic efficacy of PCV treatments: one study found that elimination of a polypoidal lesion's circumferential hyperautofluorescent ring was highly associated with resolution of that polypoidal lesion after ranibizumab treatment, PDT, or a combination of both therapies.[45]

On FFA, key characteristics of PCV are BVNs of vessels terminating in grape-like clusters of polypoidal lesions and a lower level of "leakiness" in affected vessels compared with typical exudative AMD. FFA can be used to exclude other variants of exudative AMD, but it achieves a lesser resolution of the choroidal vasculature than ICGA (Fig. 5) and is unable to visualize sub-RPE structures, including polypoidal lesions. In addition, because FFA is associated with more fluorescein dye leakage than is ICGA, PCV lesions visualized on FFA appear larger than those visualized with ICGA.[46]
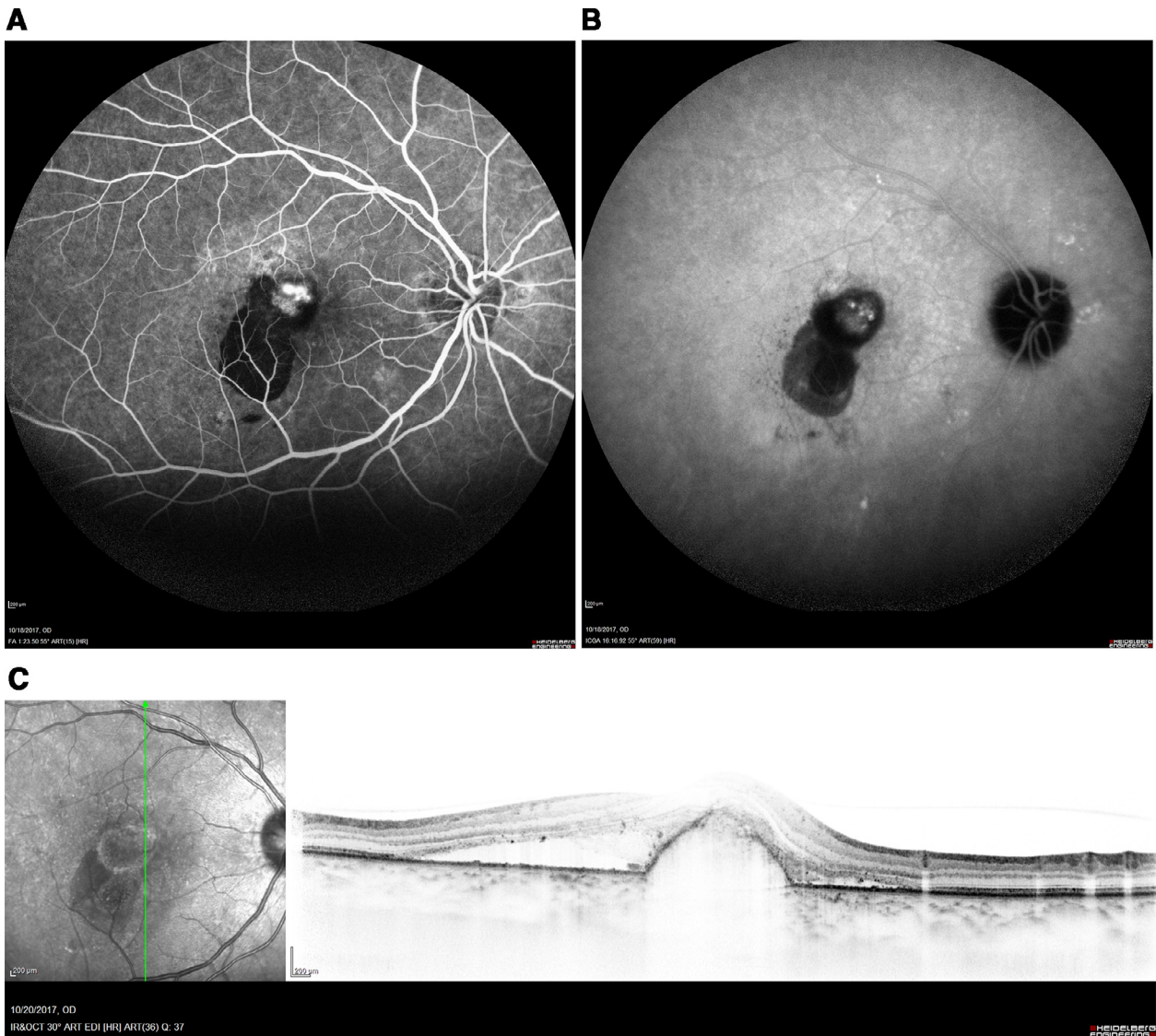
A

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Fig. 1—(A) Fundus fluorescein angiography shows blocked hypofluorescence from the subretinal blood and focal hyperfluorescence at the macula. (B) Late indocyanine green angiography shows several polypoidal lesions at the macula. Other clusters of polypoidal lesions were along the temporal arcade and nasal retina. (C) Optical coherence tomography shows peaked pigment epithelial detachment with a large amount of subretinal fluid. Images courtesy of Dr. Lam.

ICGA is not used frequently in Canada due to issues of cost and availability. BVNs with single or multiple polypoidal lesions are generally well defined in early phase ICGA, and subretinal nodular hyperfluorescence typically appears within the first 5 minutes and persists into the late phase. Video or sequential photograph review can show pulsatile lesions and feeder vessels, which raise suspicion for PCV. ICGA can also be used as a definitive test when the diagnosis is uncertain. In addition, ICGA often identifies asymptomatic quiescent polypoidal lesions in the fellow eyes of PCV patients.[47]

Multispectral imaging (MSI) is a new technology that can visualize the choroidal and retinal vasculature without intravenous dye injections. MSI works by capturing image data at specific frequencies across the electromagnetic spectrum and creating a series of *en face* fundal spectral sections throughout the entire chorioretinal thickness. By

combining the frequencies that interact with oxyhemoglobin, the system illuminates areas with relatively more oxyhemoglobin more brightly than areas with less.

A small prospective study of patients with a clinical diagnosis of treatment-naïve PCV compared MSI (obtained with a digital multispectral ophthalmoscope) with fundus photography, FFA, ICGA, and OCT.[48] MSI was found to have a sensitivity of 93.8% and a specificity of 100% for identifying typical PCV with both BVNs and polypoidal lesions.

Case Study #1

This 67-year-old man presented with sudden-onset metamorphopsia and blurring in the left eye, beginning 2 weeks previously (Figs. 6 and 7). His visual acuity was 20/40 in the right eye and 20/50 in the left.
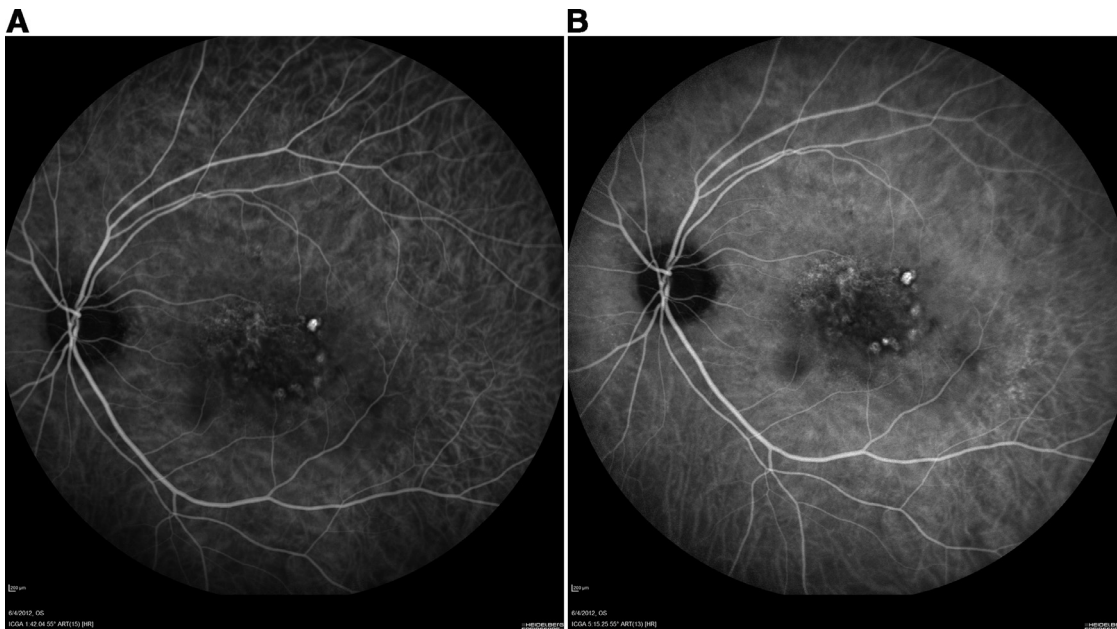
Fig. 2—(A) Midphase and (B) late-phase fundus fluorescein angiography/indocyanine green angiography show a branching vascular network with polypoidal lesions arranged in the pattern referred to as "pearls on a string." Images courtesy of Dr. Lam.
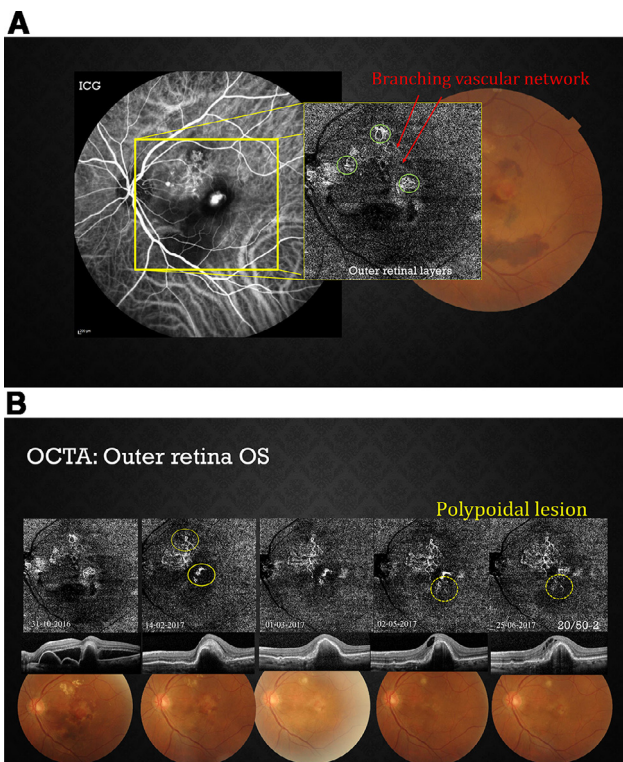

Fig. 3—(A) Indocyanine green angiography and colour fundus photographs confirm the presence of polypoidal choroidal vasculopathy polypoidal lesions. Optical coherence tomography–angiography (OCT-A) in the centre shows 3 polypoidal lesions (green circles) at the outer retinal layer. (B) Sequential OCT-A images show regression of the polypoidal lesions on March 1, 2017, and recurrence on May 2, 2017. Images courtesy of Dr. Pear Pongsachareonnont.

Case Study #2

This 49-year-old Vietnamese female was receiving cetirizine, lansoprazole, risperidone, clonazepam, escitalopram, and thyroid medication when she presented. Before these images (Figs. 8−11) were taken, she received bevacizumab.

Treatment

Untreated, symptomatic PCV may lead to severe vision loss, which may be acute (usually secondary to spontaneous rupture of polypoidal lesions, in turn leading to submacular hemorrhage causing scotoma or even breakthrough vitreous hemorrhage) or progressive (with metamorphopsia due to the accumulation of subretinal fluid and exudates around the polypoidal lesion).[49]

About half of patients with nonacute untreated PCV will undergo spontaneous remission of polypoidal lesions,[50] but in the remainder, repeat bleeding and leakage will eventually result in RPE and photoreceptor degeneration, scarring, and irreversible visual loss. There is no reliable way to know which course the condition will take in a given patient, although there is some evidence that grape-like clusters of polypoidal lesions indicate a likelihood of progressive loss due to a higher bleeding risk.[50,51] A retrospective study of Chinese patients with untreated PCV found a mean loss of 3.1 Snellen lines over 28.2 months of follow-up and a deterioration of acuity to 20/200 or worse in more than 75% of patients.[52] Given this evidence of the high risk of vision loss in untreated symptomatic PCV, active intervention is strongly indicated.
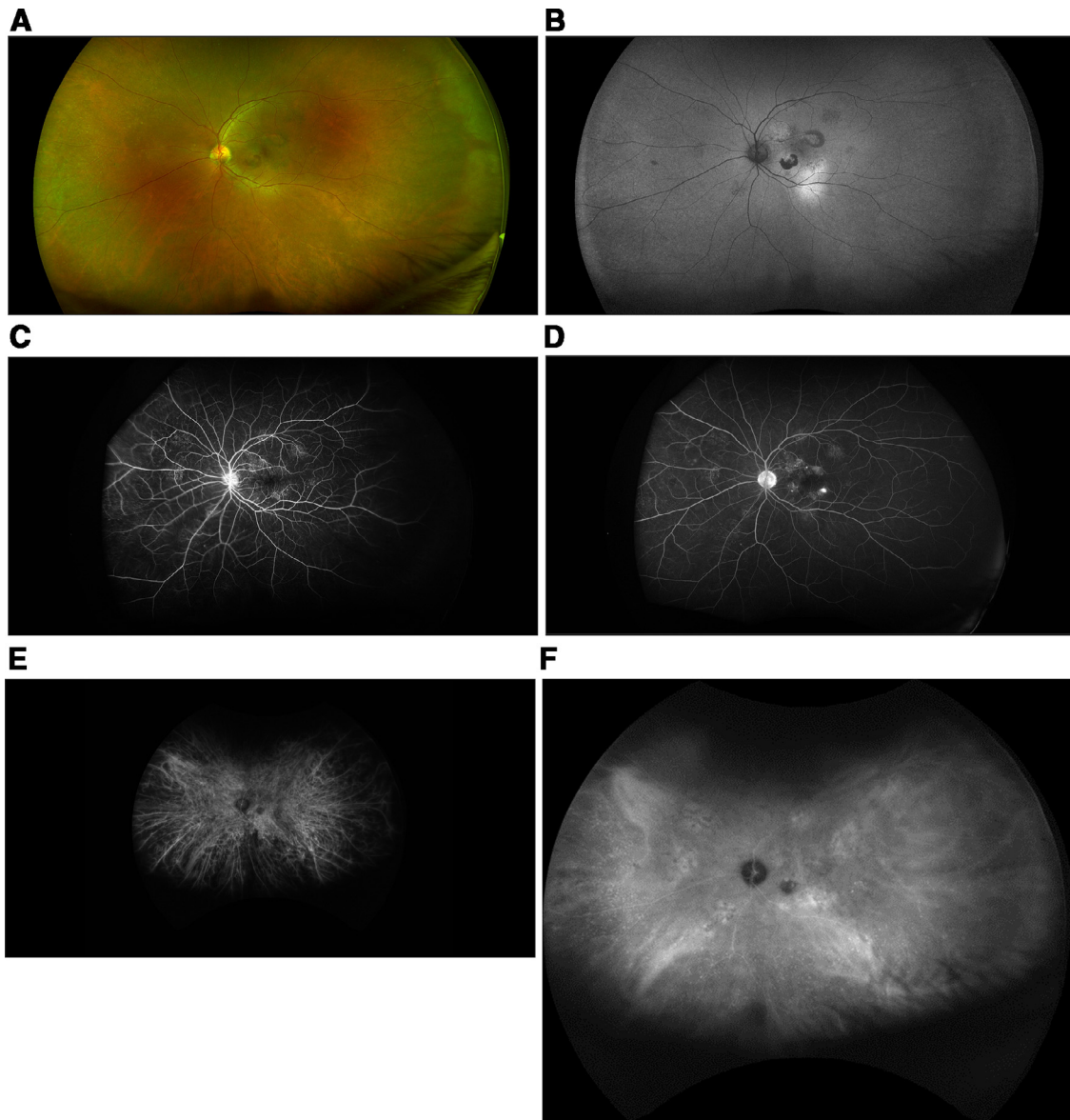
Fig. 4—(A) Ultra-widefield fundus photograph shows polypoidal lesions and subretinal hemorrhage surrounding the macula. (B) Ultra-widefield fundus autofluorescence shows hypofluorescence from the subretinal hemorrhage. (C, D) Ultra-widefield fundus fluorescein angiography shows multiple foci of window hyperfluorescence at the macula and the nasal retina. Several different sizes of polypoidal lesions surround the macula. (E, F) Ultra-widefield indocyanine green angiography shows central areas of early hypocyanescence near the macula and late hypercyanescence with polypoidal lesions. Images courtesy of Dr. Wong.

Anti-VEGF Therapy

Anti−VEGF agents have been available in Canada since 2005 and currently include bevacizumab (approved in 2005 as a colorectal cancer treatment but used off-label for ophthalmologic indications), ranibizumab (2007), and aflibercept (2013). Early studies found that anti-VEGF therapy reduced subretinal fluid and caused vision stabilization in PCV, although choroidal vascular changes on ICGA often persisted.[53−55]

A number of more recent randomized trials have examined the efficacy of available anti-VEGFs as monotherapy or in combination with PDT, although there have been no head-to-head clinical trials comparing anti-VEGF agents in PCV. The LAPTOP trial examined the effect of ranibizumab monotherapy on visual acuity, comparing PDT monotherapy with 0.5 mg ranibizumab (monthly for 3 months then prn) in 93 patients with treatment-naïve PCV.[56] The BCVA results were significantly better in the ranibizumab arm and this difference persisted at the 5-year follow-up.[57]

EVEREST I compared PDT alone and in combination with ranibizumab with ranibizumab monotherapy in PCV, finding that both PDT arms were superior to ranibizumab alone in terms of ICGA-assessed complete polypoidal lesion regression at 6 months.[58] Because EVEREST I was not
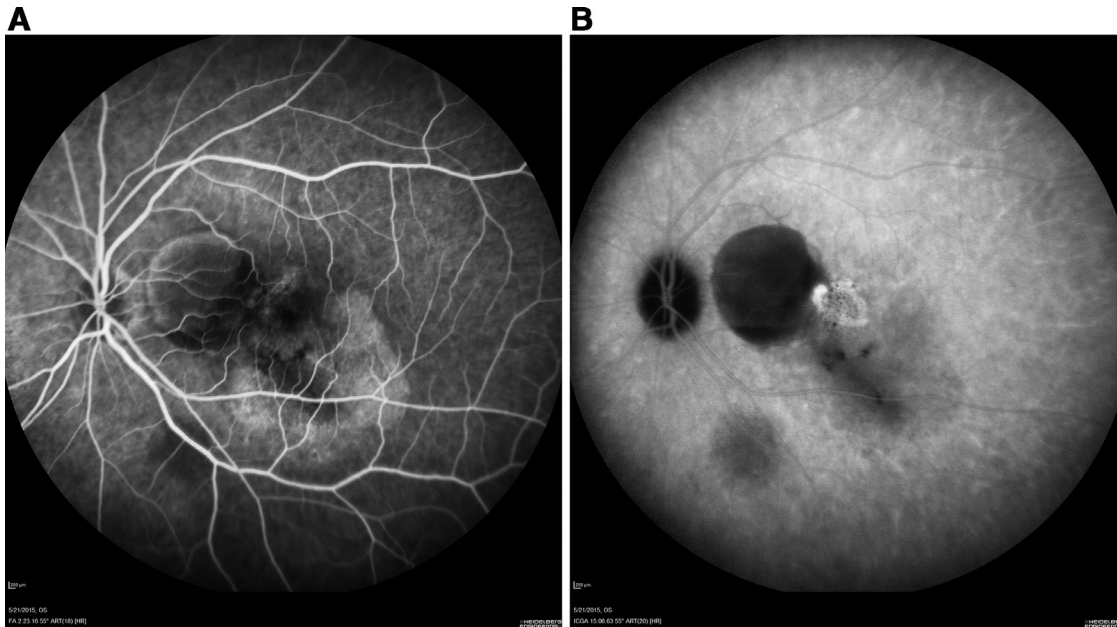
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B

Fig. 5—(A) Fundus fluorescein angiography shows pooling hyperfluorescence nasal to the macula and late staining at temporal to the macula. (B) Late indocyanine green angiography shows polypoidal lesions within the pigment epithelial detachment with an adjacent branching vascular network. Images courtesy of Dr. Lam.

powered to determine differences in best-corrected visual acuity (BCVA), EVEREST II was done to compare the combination of PDT and ranibizumab with ranibizumab alone.[59]

In EVEREST II, all patients received 3 monthly doses of ranibizumab followed by prn ranibizumab according to the protocol-specific retreatment criteria.[59] All patients also received either PDT or a sham treatment on day 1; after 3 months, PDT or sham PDT was administered on a prn basis

Fig. 6—Indocyanine green angiography shows a single polypoidal lesion at the fovea. Image courtesy of Dr. Lam.

according to retreatment criteria. At 12 months, mean change in BCVA from baseline was 8.3 letters in the combination arm and 5.1 in the monotherapy arm ($p = 0.01$ for the difference) with a greater difference in patients with worse visual acuity at baseline. Combination therapy was also superior in terms of complete polypoidal lesion regression at 12 months (achieved in 69.3% of combination therapy participants vs 34.7% of monotherapy patients, $p < 0.001$) while requiring fewer ranibizumab injections (mean 4.0 vs 7.0 in the monotherapy arm).

At 24 months, mean change in BCVA from baseline had further improved in both groups: to 9.6 letters in the combination arm and 5.5 in the monotherapy arm.[59] Complete polypoidal lesion regression at 24 months was 56.6% in the combination therapy arm, compared with 26.7% in the monotherapy arm. In addition, fluid-free retinas were achieved by 69.6% of combination therapy patients at month 24, compared with 47.1% of monotherapy patients.

PCV data from the REAL study support the EVEREST II results. REAL examined patients with neovascular AMD treated with ranibizumab 0.5 mg, some of whom had been previously treated. A retrospective subgroup analysis looked at the efficacy and safety results in 58 patients determined at baseline to have PCV, of whom 47 received ranibizumab and 11 received ranibizumab plus PDT.[60] In the monotherapy group, visual acuity at 12 months improved by 1.1 ± 17.8 letters, whereas in the combination therapy group it improved by 14.0 ± 9.2 letters ($p = 0.0009$ vs baseline). These results suggest that additional benefits can be seen with the addition of PDT to ranibizumab.

VAULT was an interventional case series in which 40 treatment-naïve PCV patients were given aflibercept (2 mg)
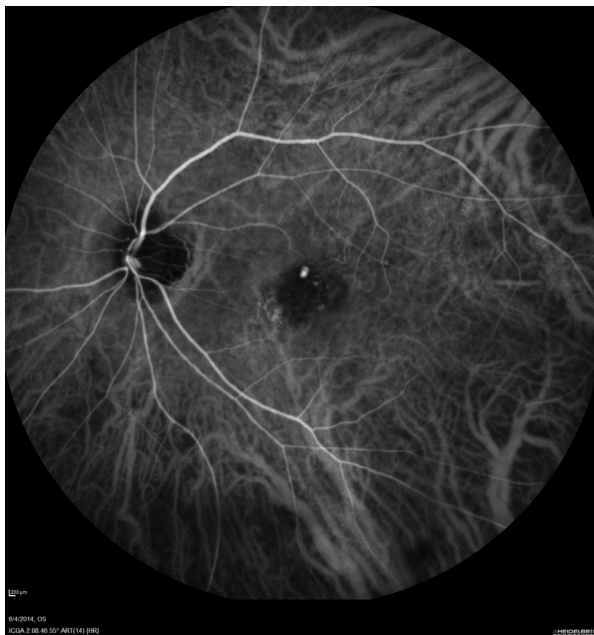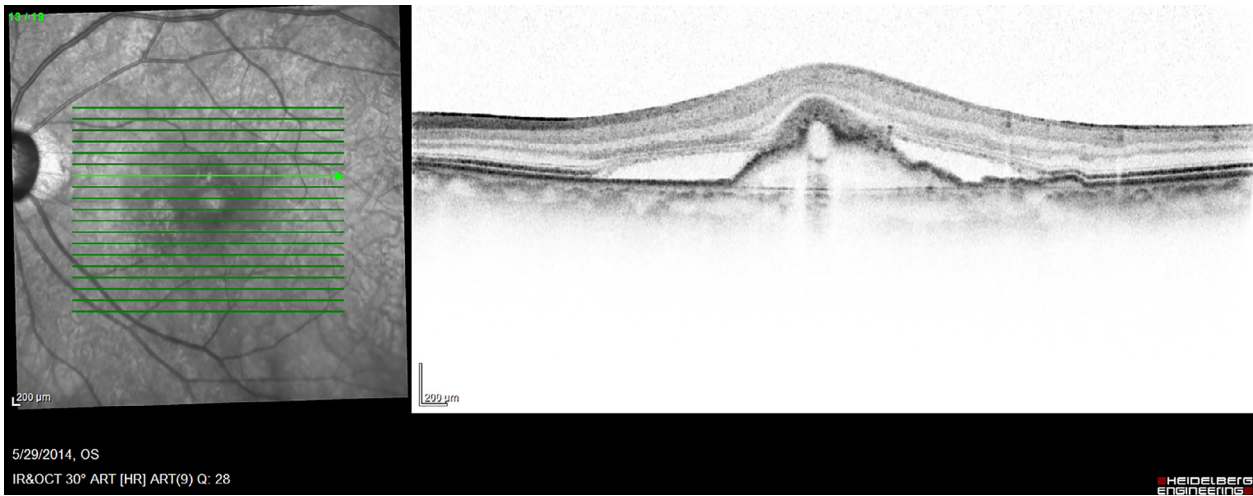
Fig. 7—Optical coherence tomography shows a peaked pigment epithelial detachment with moderate subretinal fluid. Image courtesy of Dr. Lam.

monthly for 3 months and then every 2 months thereafter.[61] At 12 months, 88% of eyes had maintained BCVA, with an average BCVA significantly higher than at baseline. Mean central subfield macular thickness (CSMT) was significantly lower at 12 months than at baseline. However, one-third of eyes had a fluid recurrence or increase at 6 months, and these patients had a significantly lower vision gain at 12 months.

Unlike the EVEREST studies, PLANET had no PDT-only arm, used fixed-dose rather than prn anti-VEGF therapy, and combined anti-VEGF therapy with rescue instead of mandated PDT.[62] Subjects were similar to those involved in EVEREST II with the exception of age ($\geq$50 years compared with $\geq$18 years in EVEREST II) and baseline visual acuity (which was lower in PLANET subjects). All patients received 3 monthly doses of aflibercept, and then those meeting rescue criteria (6% of randomized subjects as of Week 12) were randomized to receive active or sham PDT in addition to monthly aflibercept. Those who did not meet rescue criteria received aflibercept every 8 weeks during the first year and at least every 12 weeks thereafter (treat-and-extend). When the rescue criteria were no longer met in the rescue group, injection intervals were gradually extended to 8 weeks. The goal was to determine whether rescue PDT is required for patients receiving optimal doses of aflibercept.

At 12 months, patients in both study arms had gained more than 10 letters (10.8 in the active rescue group and 10.7 in the monotherapy group) and reduced CSMT by similar amounts (143.5 and 137.7 μm, respectively). More than 80% of patients in both study arms had no polypoidal lesions
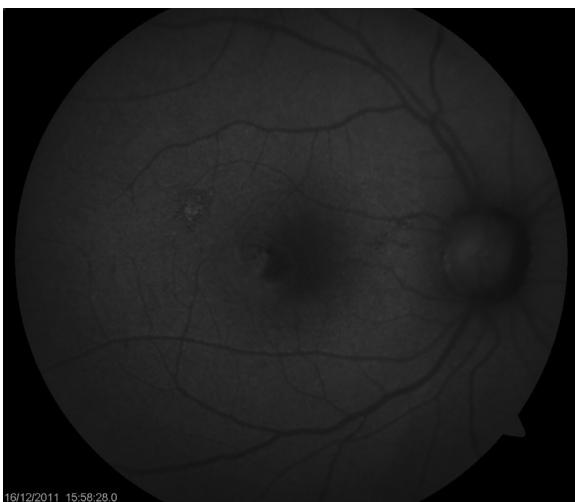

Fig. 8—Fundus autofluorescence photograph shows a patch of hypoautofluorescence with a ring of hyperautofluorescence located temporal to the fovea. It was associated with an adjacent patch of hyperautofluorescence, and another one further temporally. Image courtesy of Dr. Lam.
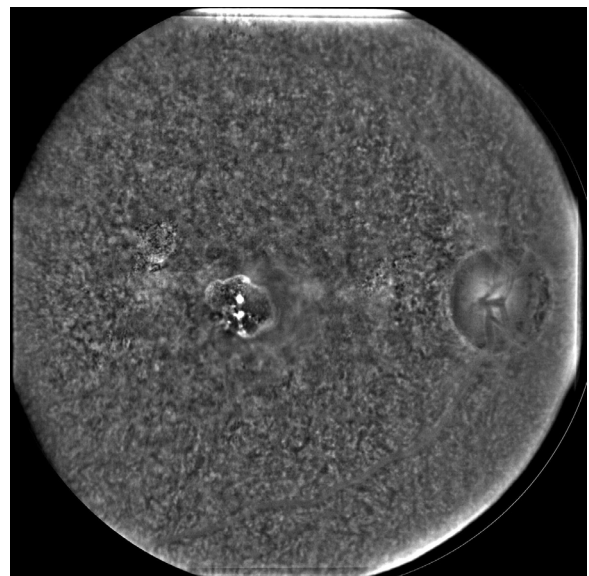

Fig. 9—Multispectral imaging shows a ring of hyperfluorescence with multiple hyperfluorescence spots at its centre, consistent with polypoidal lesions. Image courtesy of Dr. Lam.

Fig. 10—Colour fundus photograph shows pigment epithelial detachments involving the temporal aspect of the fovea. Drusen of different size present further temporally. Image courtesy of Dr. Lam.

with leakage. Among the less than 15% of patients who required rescue over 52 weeks (14.3% in the active PDT rescue group and 12.1% in the monotherapy group), vision gains were similar in both study arms, but mean changes in CSMT were greater in the active PDT arm, as were the proportion of subjects with no active polypoidal lesions (90.0% vs 31.3% in the monotherapy arm) and the proportion of subjects with complete polypoidal lesion regression (44.4% vs 6.7%).

At 96 weeks, PLANET continued to show mean BCVA improvements in both study arms; however, the monotherapy group maintained the BCVA gains of the first year through week 96, whereas the active PDT rescue group lost nearly 5 letters between week 52 and week 96.[63] Mean CSMT changes from baseline to week 96 showed no difference between the groups. The percentage of patients with no active polypoidal lesions at week 96 was 82.1% in the monotherapy group and 85.6% in the rescue group. Although these results demonstrate that aflibercept monotherapy can achieve clinically meaningful responses for most people with PCV, the low numbers of patients requiring rescue PDT means that the benefits of adding PDT in the general PCV population cannot be properly determined through this study.

Like PLANET, the ATLANTIC study had no PDT-only arm and combined anti-VEGF therapy with rescue PDT. However, ATLANTIC involved a solely Caucasian population.[64] Fifty patients with treatment-naïve PCV received monthly aflibercept for 3 months then were randomized at week 16 into PDT or sham PDT groups. PDT or sham PDT was performed at weeks 16, 28, and 40 in the presence of active polypoidal lesions. After week 16, the aflibercept injection schedule depended on the presence or absence of macular fluid on OCT: if present, the interval between injections was decreased by 2 weeks (to a minimum of 6

weeks); if absent, the interval was increased by 2 weeks (to a maximum of 12 weeks).

Twenty-one patients had active polypoidal lesions at week 16 and received PDT or sham PDT.[65] Change in BCVA from baseline to week 52 (a primary endpoint) was between 6 and 7 letters in both groups with no statistically significant difference. The other primary endpoint, polypoidal lesion regression at week 52 (as assessed by ICGA), also showed no significant differences between groups, although a decrease in the mean area of polypoidal lesions was seen in the PDT group but not in the sham PDT group. This supports PLANET's conclusion that aflibercept monotherapy can produce clinically meaningful results for many people with PCV, including Caucasians.

Other studies have confirmed the efficacy of aflibercept in combination with PDT. In a single-arm, prospective study, 26 treatment-naïve PCV patients received a single dose of aflibercept (2.0 mg) and then standard PDT after a week of induction therapy.[66] No additional treatment was applied for 3 months; at 3, 12, and 24 months, additional aflibercept could be applied at the physician's discretion in cases with residual or worsening exudative lesions at the macula. If polypoidal lesion regression was not complete at that time, PDT was also given. Over 24 months, the mean BCVA improved by 0.11 logarithm of the minimum angle of resolution (logMAR) units from baseline ($p < 0.01$), and the mean central retinal thickness significantly decreased ($p = 0.001$). Complete regression of polypoidal lesions was achieved by 15 out of 20 eyes at 12 months and 11 out of 20 eyes at 24 months.

Finally, a small study has shown that aflibercept is effective as a second-line therapy in PCV patients with exudation but without active polypoidal lesions after prior treatment with PDT or another anti-VEGF.[67] Forty patients meeting these criteria were given aflibercept monthly for 3 months, and then every 2 months in the maintenance phase. Mean visual acuity improved from 61.5 ± 11.1 letters at baseline to 68.1 ± 13.6 letters at 14 months ($p = 0.001$). Factors associated with better visual outcomes were better vision and smaller lesion size at baseline, and absence of an inner retinal cyst after induction therapy.

Photodynamic Therapy

PDT is associated with a high cost and the need for special equipment (including ICGA) and training. In a patient on anti-VEGF therapy who does not meet rescue criteria (such as lack of response in BCVA, new or persistent fluid, or evidence of active polypoidal lesions), the addition of mandated PDT may increase the risk of poor outcomes, such as the loss of long-term vision gains due to choroidal ischemia and RPE atrophy, or the development of new or recurrent polypoidal lesions. Still, questions remain about the potential benefit of adding PDT to aflibercept initiation rather than as rescue, and whether half-fluence or selective PDT could prove less damaging and show some benefit.
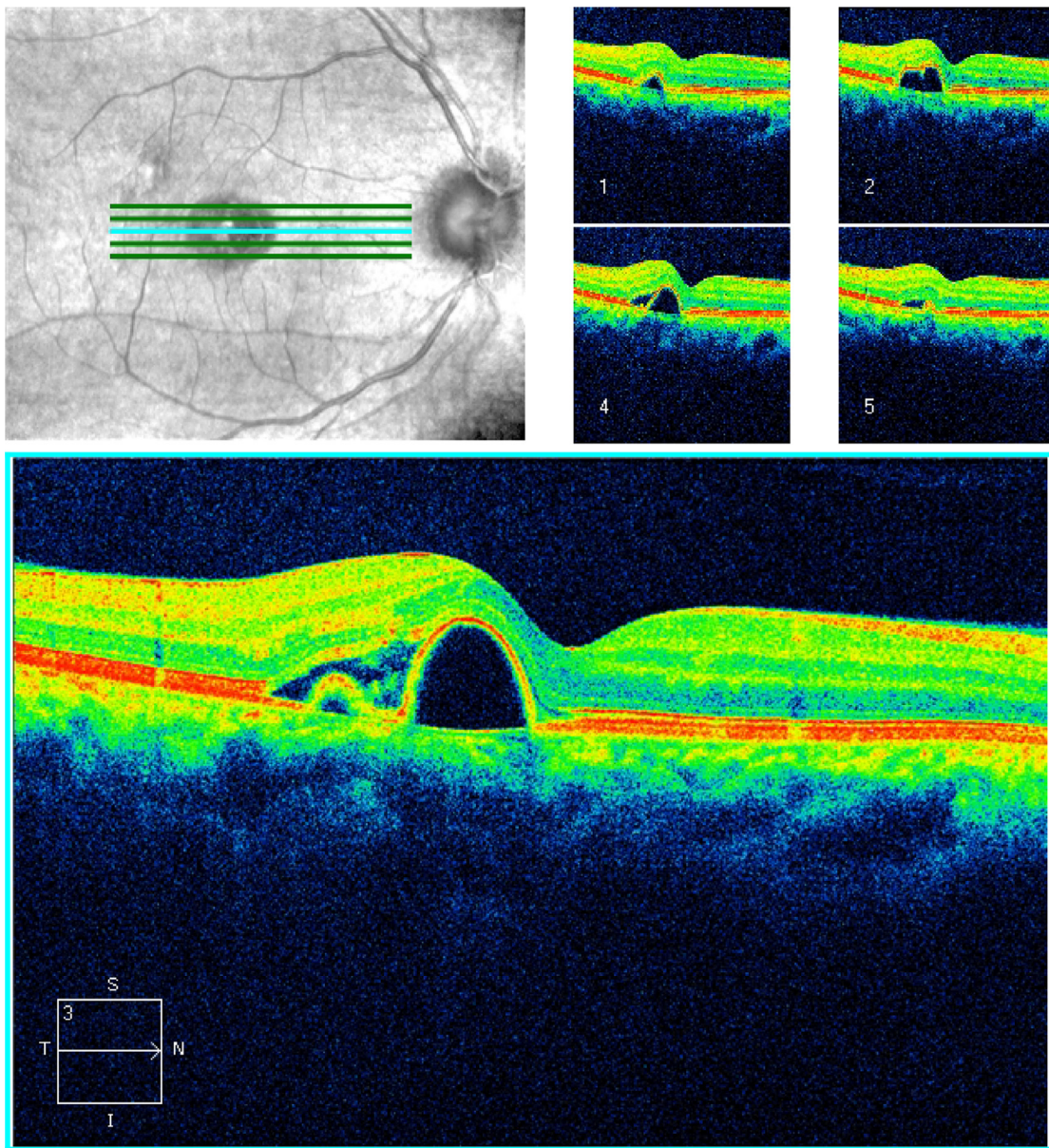
Fig. 11—Optical coherence tomography shows thumb-shaped pigment epithelial detachments of different sizes at the fovea associated with subretinal fluid and hyper-reflective material. Image courtesy of Dr. Lam.

PDT is seldom recommended alone in PCV, although juxtafoveal polypoidal lesions without associated exudation may be treated with PDT to prevent hemorrhage and exudation. It is also appropriate in cases that are recalcitrant to anti-VEGF loading.

It is also possible that low-dose (reduced-fluence) PDT may have a role in future treatment. Two small studies of reduced-fluence PDT in combination with ranibizumab have found that the reduced laser exposure minimized the risks of PDT-induced adverse events while improving BCVA and decreasing macular thickness.[68,69] Another study examined half-fluence PDT; results suggested that it is effective for single polypoidal lesions and may reduce harm to the RPE and choriocapillaris.[70]

Treating PCV in Canada

There is no clear evidence at this time to support first-line agent recommendations for this indication. In light of the PLANET results showing that aflibercept monotherapy achieved good responses in the majority of PCV patients, one option could be treatment with 3 monthly doses of aflibercept. If the patient responds, treatment can be continued on a bimonthly basis; if not, monthly aflibercept can be tried because rescue PDT apparently provides no additional benefit. At present, aflibercept combination therapy with PDT from the start has not been evaluated in clinical trials; therefore, it is unclear if combination therapy is superior to aflibercept monotherapy. Based on the EVEREST II results,

ranibizumab with concurrent PDT would be an equally appropriate option for those with access to PDT. Some may consider ranibizumab monotherapy as an option based on the positive results of LAPTOP and the lack of a head-to-head comparative study with aflibercept monotherapy. In all cases, a treat-and-extend strategy can be used (as in the second year of the PLANET study) to extend intervals between treatments as long as the patient remains asymptomatic, because there is a high rate of recurrence after stopping treatment.

Of course, some presentations are more difficult to treat. For example, there is no clear consensus on whether to treat a "pearls on a string" presentation without subretinal fluid, because the patient's prognosis is better in the absence of sub-retinal fluid.

Conclusions

Patients with PCV can be of any ethnicity and make up at least 7.8% of those with exudative AMD, although this is likely an underestimate. In Canada, underdiagnosis of PCV may be a result of the underuse of ICGA (perhaps due to limited access) or under-recognition of the diagnosis, especially among non-Asian patients. Such underdiagnosis is significant because misdiagnosis carries the risk of unsatisfactory clinical outcomes that could have been avoided.

One reason for the difficulty in diagnosing PCV is that its presentation can vary widely. Hemorrhagic, exudative, and quiescent subtypes of PCV display differing clinical and imaging characteristics. Although ICGA is the gold standard for diagnosis, the combination of the latest OCT technology and colour fundus photography can help to identify PCV without invasive imaging.

Without treatment, symptomatic PCV may result in severe acute or progressive vision loss. Anti-VEGF agents are the foundation of current therapy, as monotherapy or in combination with PDT. The results of recent clinical trials have demonstrated that the addition of mandated PDT increases the efficacy of ranibizumab monotherapy (EVEREST II), but that rescue PDT does not increase the benefit associated with aflibercept monotherapy (PLANET).

Canada's population is ethnically diverse. The authors hope that this article will encourage Canadian ophthalmologists to be alert for the diagnosis of PCV in all ethnic groups, as well as providing a review of its identification and current evidence-based treatments.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcjo.2019.10.011.

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Footnotes and Disclosure

From the *Department of Ophthalmology, The University of Hong Kong, Hong Kong, Hong Kong; †Department of Ophthalmology and Vision Sciences, University of Toronto, Unity Health Toronto, St. Michael's Hospital, Toronto, Ont.; ‡Vitreous Retina Macula Specialists of Toronto, Toronto, Ont.

Correspondence to Wai-Ching Lam, MD, Department of Ophthalmology, The University of Hong Kong, Room 301, Block B, Cyberport 4, 100 Cyberport Road, Hong Kong, Hong Kong. waichlam@hku.hk