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Anti–Vascular Endothelial Growth Factor Resistance in Exudative Macular Degeneration and Polypoidal Choroidal Vasculopathy

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Purpose: To evaluate the prevalence of polypoidal choroidal vasculopathy (PCV) in different ethnic populations and to determine the prevalence of PCV in eyes with exudative age-related macular degeneration (AMD) that is sensitive and resistant to anti–vascular endothelial growth factor (VEGF) therapy.

Design: Retrospective chart review.

Participants: Two hundred fifty-three eyes of 221 patients with exudative AMD.

Methods: Baseline data were collected on all eyes diagnosed with exudative AMD, which included ethnic data. Polypoidal choroidal vasculopathy was diagnosed using indocyanine green angiography (ICGA) with the scanning laser ophthalmoscope. Exudative AMD eyes were separated into 2 groups: anti-VEGF–resistant eyes with persistent subretinal fluid, subretinal hemorrhage, or macular edema after 4 anti-VEGF injections and anti-VEGF–sensitive eyes defined as eyes without residual disease activity. The prevalence of PCV was determined in each group based on ICGA.

Main Outcome Measures: Prevalence of PCV in exudative AMD, and in different ethnic populations, and prevalence of anti-VEGF resistance in eyes with and without PCV.

Results: Exudative AMD was diagnosed in 253 eyes of 221 patients. Polypoidal choroidal vasculopathy was noted to have a prevalence of 45.1% (114/253 eyes) in the overall population. Polypoidal choroidal vasculopathy was noted in 51.6% (81/157) of eyes with wet AMD in Asians, 31.9% (23/72 eyes) of eyes with wet AMD in white persons, and 28.6% (4/14 eyes) in a small group of Pacific Islanders. Polypoidal choroidal vasculopathy was diagnosed in 50% (60/120 eyes) of eyes in the anti-VEGF–resistant group, which is more prevalent than the 30.2% (29/96 eyes) in the anti-VEGF–sensitive group ($P < 0.001$).

Conclusions: Polypoidal choroidal vasculopathy is more prevalent in Asian patients with exudative AMD, but is more prevalent than generally recognized in white patients. Polypoidal choroidal vasculopathy is more prevalent in anti-VEGF–resistant eyes in both white and Asian patients, which could help to predict therapeutic response. *Ophthalmology Retina 2019;3:744-752 © 2019 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.ophthalmologyretina.org.

Antiangiogenic therapy with anti–vascular endothelial growth factor (VEGF) agents has become the standard of care for the treatment of exudative age-related macular degeneration (AMD). Clinical trials have shown that regular intravitreal injections of anti-VEGF drugs result in marked resolution of leakage, edema, and bleeding with improved visual results.[1–3] This efficacy of anti-VEGF drugs has improved the clinical course and visual prognosis remarkably for patients with exudative AMD. However, some eyes with exudative AMD show resistance to anti-VEGF drugs with persistent leakage, edema, or blood despite therapy. These eyes tend to show a worse visual prognosis. In managing patients with exudative AMD, a marker to identify patients predisposed to anti-VEGF resistance would be useful to guide therapy.

Choroidal neovascularization is responsible for exudative AMD and may be caused by different subtypes. The Gass classification[4] used an anatomic definition of choroidal neovascularization, with type I located below the retinal pigment epithelium (RPE), type II located above the RPE, and type III including an intraretinal component of neovascularization also termed *retinal angiomatous proliferation*.[5] Polypoidal choroidal vasculopathy (PCV) has a characteristic anatomic pattern of subretinal neovascularization with polypoidal or aneurysmal dilations with or without a branching vascular network (BVN) that is imaged best on indocyanine green angiography (ICGA).[6] Point-to-point localization of the PCV lesions seen on ICGA to OCT shows that the aneurysmal dilations and BVN are

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below the RPE and above Bruch's membrane.[7] Thus, PCV is not in the choroid and is a variant of type I subretinal neovascularization causing exudative AMD.

Despite the dramatic success of anti-VEGF drugs in exudative AMD, persistent or recurrent fluid on OCT is not uncommon on extended follow-up. In the Comparison of Age-Related Macular Degeneration Treatments Trials[8] for exudative AMD at 2 years, persistent fluid was present on OCT in 53.2% of the monthly ranibizumab group and 68.8% of the monthly bevacizumab group, with even higher percentages of fluid on OCT in the corresponding pro re nata groups.[9] In patients with persistent fluid after treatment with anti-VEGF drugs for exudative AMD, there have been case reports demonstrating the presence of PCV on ICGA in these patients with neovascular AMD, suggesting that PCV could be a phenotypic marker for anti-VEGF resistance.[10,11]

To evaluate this hypothesis of higher prevalence of PCV in anti-VEGF–resistant eyes in a white population in Switzerland, Hatz and Prünte[12] evaluated 202 eyes with AMD in a retrospective study and showed that the prevalence of PCV is increased in eyes that respond poorly to ranibizumab monotherapy (21.5% compared with 3.8% of treatment-responsive eyes). They also demonstrated that as soon as the diagnosis of PCV was made using ICGA, the initiation of combination therapy with photodynamic therapy (PDT) and anti-VEGF injection is beneficial. Their study supports the idea of anti-VEGF resistance in PCV, but the criteria were based on a pro re nata mode of anti-VEGF treatment, which is the standard of care in Switzerland. To evaluate anti-VEGF resistance using a more widespread approach to anti-VEGF treatment with an initial loading dose of sequential injections, we defined anti-VEGF resistance based on persistent disease activity using OCT after 4 sequential continuous anti-VEGF injections. Loading-dose therapy often is begun with 3 or 4 sequential anti-VEGF injections, so anti-VEGF resistance was defined in this study as persistent SF, subretinal hemorrhage, or macular edema after 4 sequential injections. As in the study by Hatz and Prünte, this was performed in a retrospective manner to evaluate further the observation that PCV is more prevalent in anti-VEGF–resistant eyes. In addition, the population diversity of Hawaii allowed the ability to analyze this association in both white and Asian patients.

Subretinal aneurysmal dilations in subretinal neovascularization (PCV) are important to diagnose because of potential alternatives in treatment for this subtype of exudative AMD. A meta-analysis by Tang et al[13] included 9 studies that compared ranibizumab monotherapy, photodynamic therapy (PDT) monotherapy, and combination therapy with PDT and ranibizumab. Overall, combination therapy demonstrated an improved synergistic effect on regressing polyps and improving visual acuity (VA) over either therapy alone. More recently, the EVEREST II trial demonstrated that combination therapy is superior to ranibizumab monotherapy for improving vision and regression of polypoidal aneurysmal lesions, while requiring approximately one third fewer injections at 12 months.[14] These findings were confirmed at the 2-year follow-up with better vision results and only one half of intravitreal injections being necessary in the combination PDT plus ranibizumab group (Koh A, et al. Everest 2 trial: 2-year results. Paper presented at: Asia Pacific Vitreoretinal Society, December 9, 2017; Kuala Lampur, Malaysia).

Although PCV was described first by Yannuzzi[15] and Yannuzzi et al[16] in white and black patients, this subtype of exudative age-related AMD has been reported to have the highest prevalence in Asian populations.[17] The clinical characteristics of PCV vary in different ethnic groups. In black patients, PCV has larger caliber vessels, female predominance, and a predominantly peripapillary location.[15,16] In Asian patients, PCV more frequently is located in the macula with a male predominance.[17] Although PCV was believed to be less common in white patients based on studies using ICGA with fundus flash camera screening, with prevalence rates ranging from 4% to 8%,[18,19] a higher prevalence of PCV in white patients has been noted when ICGA is performed using the scanning laser ophthalmoscope, with 24.5% of patients of predominantly European ancestry with exudative AMD showing PCV.[20,21]

The purpose of this study was to evaluate the prevalence of PCV in eyes with presumed exudative AMD resistant to intravitreal anti-VEGF injection monotherapy compared with eyes with exudative AMD with good sensitivity to initial intravitreal anti-VEGF injection monotherapy. The definition of anti-VEGF resistance is not universally well accepted, but for this study, anti-VEGF resistance was defined anatomically as the persistence of macular edema, subretinal hemorrhage, or subretinal fluid (SF) after 4 consecutive and sequential anti-VEGF injections. Because the clinical characteristics of PCV in Asian and white patients differ and because PCV is more common in Asian patients, the prevalence rates of PCV in anti-VEGF–resistant eyes also were compared in different ethnic groups.

Methods

This study was a retrospective chart review of all consecutive patients seen on Oahu and Kauai by Retina Consultants of Hawaii and the Hawaii Macula and Retina Institute for treatment of exudative AMD from January 2010 through December 2016. The Western Institutional Review Board exempted this study from institutional review board approval because of its retrospective design (identifier, 1-987382-1). This study adhered to the policies set forth by the Health Insurance Portability and Accountability Act and the Declaration of Helsinki. As this was a retrospective study, patients did not sign an informed consent form specifically for this study.

The patients were seen and diagnosed with exudative AMD by 3 retinal specialists (GTK) at Retina Consultants of Hawaii and the Hawaii Macula and Retina Institute. All patients underwent a baseline ophthalmic examination, including best-corrected VA, slit-lamp examination, and dilated fundus examination with a 90-diopter lens. The data collected retrospectively included basic demographics, fundus findings, affected eye, family history, prior ocular surgery or laser treatment, duration of disease, systemic medical history, date of onset, number of intravitreal anti-VEGF injections, intravitreal injection medication (bevacizumab, aflibercept, and ranibizumab), presence of SF, presence of macula edema, and presence of subretinal hemorrhage. Exclusion criteria included concomitant retinal diseases including diabetic retinopathy, vascular occlusion, myopic degeneration, or inflammatory disease; prior focal laser therapy or prior PDT; major trauma; previous vitrectomy or intraocular surgery except for

uncomplicated cataract surgery; and prior intravitreal steroid injection. If follow-up examination and OCT were not available after the fourth sequential anti-VEGF injection, then these patients were excluded from the anti-VEGF resistance study.

The charts also were reviewed for the clinical diagnosis of PCV as determined using ICGA using the scanning laser ophthalmoscope (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany). Careful evaluation was given to ICGA images between 3 and 5 minutes. The visualization of aneurysmal dilations or polypoidal vascular lesions with or without a BVN were used to make the diagnosis. Confirmatory information also was obtained by B-scan OCT scanning using point-to-point localization of the lesion visualized on ICGA with the OCT B-scan characteristics at that exact location. Supplemental confirmation was obtained using en face imaging using spectral-domain OCT (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA).[21] On B-scan OCT, polyps appeared as inverted U-shaped elevations of the RPE, and the BVN appeared as shallow parallel elevations of the RPE above Bruch's membrane, also known as the double-line sign (Figure S1, available at www.ophthalmologyretina.org).[7] All diagnoses of PCV were confirmed by 1 experienced physician (GTK) trained in ICGA diagnosis and multimodal imaging for PCV.

To evaluate anti-VEGF resistance, eyes with exudative AMD were evaluated for response to initial intravitreal anti-VEGF injection monotherapy. Anti−vascular endothelial growth factor resistance was defined anatomically as persistent disease activity (macular edema, SF, or subretinal blood) after the first 4 sequential intravitreal injections, whereas anti-VEGF sensitivity was defined as resolution of macular edema, SF, or subretinal hemorrhage after the first 4 intravitreal anti-VEGF injections. Anti-VEGF−resistant eyes included eyes with persistent leakage or bleeding, and anti-VEGF−sensitive eyes achieved resolution of disease activity. The prevalence of PCV in each group was determined. Baseline characteristics of each group were compared.

IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY) was used to perform a 2-tailed 2-sample unequal variance *t* test to calculate the *P* value for central foveal thickness (CFT) and age between the 2 groups. To compare proportions between groups, the z-distribution was used for analysis. Calculations were performed using the *P* value using the normal distribution. A *P* value of less than 0.05 was considered statistically significant.

Results

Baseline Demographics for Polypoidal Choroidal Vasculopathy Prevalence Study

Overall, 253 eyes of 221 patients with exudative AMD were included in the study. In this study population in Hawaii, 157 eyes were from 141 Asian patients, 72 eyes were from 58 white patients, and 14 eyes were from 12 Pacific Islander patients. Ten eyes of 10 patients did not have a reported ethnicity or had mixed ancestry. Polypoidal choroidal vasculopathy was noted to have a prevalence of 45.1% (114/253 eyes) in the overall population, with 114 eyes diagnosed with PCV in 107 patients. Polypoidal choroidal vasculopathy was noted in 51.6% (81/157 eyes) of wet AMD eyes in Asians, 31.9% (23/72 eyes) of wet AMD eyes in white patients, and 28.6% (4/14 eyes) in a small group of Pacific Islanders. Of the 10 eyes that did not have a reported ethnicity or had mixed ancestry, 60% of eyes (6/10) were noted to have PCV.

The average age at diagnosis of PCV was 78.7 years (range, 47−98 years). The reported ethnicities included 75 Asian patients (70%), 22 white patients (21%), 4 Pacific Islander patients (3.7%), 1 Hispanic patient, and 5 patients with other or nonreported ethnicities. There were not any black patients with PCV in this patient population in Hawaii. Of the Asian patients, 36 were Japanese, 9 were Chinese, 16 were Filipino, 7 were Korean, and 7 were of unreported origin.

Of the total 107 patients with exudative AMD with PCV, 58.9% (63/107) were men. Of the total 114 patients with exudative AMD without PCV, 62.3% (71/114) were women. Men were significantly more prevalent among patients with PCV, whereas women were more prevalent among patients without PCV ($P = 0.00165$). In Asian patients, 58.7% of patients (44/75) with exudative AMD with PCV were men, whereas 63.6% of patients (42/66) with exudative AMD without PCV were women. Men were significantly more prevalent among Asian patients with PCV, whereas women were more prevalent among Asian patients without PCV ($P = 0.00818$). In white patients, 59.1% (13/22) with exudative AMD with PCV were men, whereas 69.4% (25/36) with exudative AMD without PCV were women. Men were significantly more prevalent among white patients with PCV, whereas women were more prevalent among white patients without PCV ($P = 0.03227$).

Anti−Vascular Endothelial Growth Factor Resistance Study

For this separate study of anti-VEGF resistance, patients were required to have anti-VEGF treatment and OCT data after 4 sequential intravitreal injections for exudative AMD. The baseline demographics of the anti-VEGF−resistant and anti-VEGF−sensitive groups are summarized in Table 1. The anti-VEGF−resistant group showed a statistically significant higher proportion of men (52.5% in the resistant group vs. 36.5% in the sensitive group; $P = 0.0093$),

Table 1. Baseline Characteristics and Demographics

Characteristic	Anti−Vascular Endothelial Growth Factor Resistant (n = 120)	Anti−Vascular Endothelial Growth Factor Sensitive (n = 96)	P Value
Male	63 (52.5)	35 (36.5)	0.009
Asian	73 (60.8)	62 (64.6)	0.286
White	37 (30.8)	25 (26.0)	0.220
Pacific Islander	6 (5.0)	6 (6.3)	0.345
Other race/mixed	4 (3.3)	3 (3.1)	0.466
Nonsmoker	93 (77.5)	83 (86.5)	0.046
Average age (yrs)	77.3	82.1	0.0005
Average CFT (μm)	332.9	308.9	0.085

CFT = central foveal thickness.
Data are no. (%) unless otherwise indicated.

Table 2. Prevalence of Polypoidal Choroidal Vasculopathy in Different Ethnic Groups

	Anti–Vascular Endothelial Growth Factor Resistant (n = 120)	Anti–Vascular Endothelial Growth Factor Sensitive (n = 96)	*P* Value
All races	60 (50.0)	29 (30.2)	0.001659
Asian*	41 (56.2)	23 (37.1)	0.013516
White*	16 (43.2)	4 (16.0)	0.012191
Pacific Islander*	1 (16.7)	1 (16.7)	0.5
Other race/mixed*	2 (50.0)	1 (33.3)	0.329622

Data are no. (%) unless otherwise indicated.
*Percentage calculated with baseline demographic values.

younger average age of onset (77 years in the resistant group vs. 82 years in the sensitive group; $P = 0.0005$), lower proportion of nonsmokers (77.5% in the resistant group vs. 86.5% in the sensitive group; $P = 0.046$), and larger average CFT (332.9 μm in the resistant group vs. 302 μm in sensitive group; $P = 0.016$). There was no statistically significant difference between the anti-VEGF–resistant and anti-VEGF–sensitive groups at baseline for ethnic populations, including white, Asian, Pacific Islander, and other races or mixed ethnicities (Table 1).

The anti-VEGF resistance study included 216 exudative AMD eyes (Table 2) . In the anti-VEGF–resistant group, 60 of 120 eyes (50%) were determined to have PCV on ICGA. In the anti-VEGF–sensitive group, 29 of 96 eyes (30.2%) were diagnosed with PCV on ICGA. The difference in prevalence of PCV between the 2 groups was found to be statistically significant ($P < 0.001$), indicating that eyes with anti-VEGF resistance have a higher prevalence of PCV (Table 2).

Of the AMD eyes among Asian patients, PCV was noted in 41 of 73 eyes (56.2%) in the anti-VEGF–resistant group, which is higher than the 23 of 62 eyes (37.1%) in the anti-VEGF–sensitive group ($P = 0.014$). Of the AMD eyes among white patients, PCV was noted to be higher in the anti-VEGF–resistant group, with 16 of 37 eyes (43.2%), than in the anti-VEGF–sensitive group, with 4 of 25 eyes (16%; $P = 0.012$). The prevalence of PCV in anti-VEGF resistant eyes in Asian patients was 1.5 times higher, and that in anti-VEGF–resistant eyes in white patients was 2.7 times higher (Table 2). Conversely, eyes without PCV were found to be more prevalent in the anti-VEGF–sensitive group overall, as well as in Asian and white groups (Table 3).

Because this was a retrospective study, the anti-VEGF treatment varied among the different patients. Of the 120 eyes in the anti-VEGF–resistant group, 82 eyes (68.3%) received bevacizumab, 22 eyes (18.3%) received aflibercept, and 16 eyes (13.3%) received ranibizumab. Of the 96 eyes in the anti-VEGF–sensitive group, 48 eyes (50.0%) received bevacizumab, 20 eyes (20.8%) received aflibercept, and 28 eyes (29.2%) received ranibizumab. Bevacizumab was used statistically significantly more in the anti-VEGF–resistant group ($P = 0.0031$). There was not a statistically significant difference in use of aflibercept ($P = 0.3223$). Ranibizumab use was higher in the anti-VEGF–sensitive group ($P = 0.0020$). The treatment interval average between the first and second injection was 42.3 days, that between the second and third injection was 44.1 days, and the overall treatment interval average for all 4 injections was 48.6 days.

Baseline subretinal hemorrhage was noted in 26.4% of eyes (57/216). Of the 57 eyes with initial subretinal hemorrhage, 54.4% of eyes (31/57) showed persistent subretinal hemorrhage after 4 injections and were classified into the anti-VEGF–resistant group because of the subretinal hemorrhage. However, 45.6% of eyes (26/57) with initial subretinal hemorrhage showed resolution after 4 injections, so that subretinal hemorrhage was not a determination of anti-VEGF resistance in these eyes. There was no difference between eyes with baseline subretinal hemorrhage determining anti-VEGF resistance between the 2 groups ($P = 0.349$). Initial subretinal hemorrhage in the 57 eyes was classified by size as small (<1 disc diameter), medium (1–3 disc diameters), and large (>3 disc diameters). The percentages of subretinal hemorrhage size were 50.9% (29/57) small, 26.3% (15/57) medium, and 22.8% (13/57) large. Of the overall 253 eyes, 45.1% (114 eyes) showed PCV and 54.9% (139 eyes) did not show PCV. Of the eyes with PCV, 23.7% (27/114 eyes) showed subretinal hemorrhage, whereas 29.5% of eyes (41/139 eyes) without PCV showed subretinal hemorrhage, so there was not any statistically significant difference

Table 3. Prevalence of Wet Age-Related Macular Degeneration without Polypoidal Choroidal Vasculopathy in Different Ethnic Groups

	Anti–Vascular Endothelial Growth Factor Resistant (n = 120)	Anti–Vascular Endothelial Growth Factor Sensitive (n = 96)	*P* Value
All races	60 (50.0)	67 (69.8)	0.001659
Asian*	32 (43.8)	39 (62.9)	0.013516
White*	21 (56.8)	21 (84)	0.012191
Pacific Islander*	5 (83.3)	5 (83.3)	0.5
Other race/mixed*	2 (50.0)	2 (66.6)	0.329622

Data are no. (%) unless otherwise indicated.
*Percentage calculated with baseline demographic values.

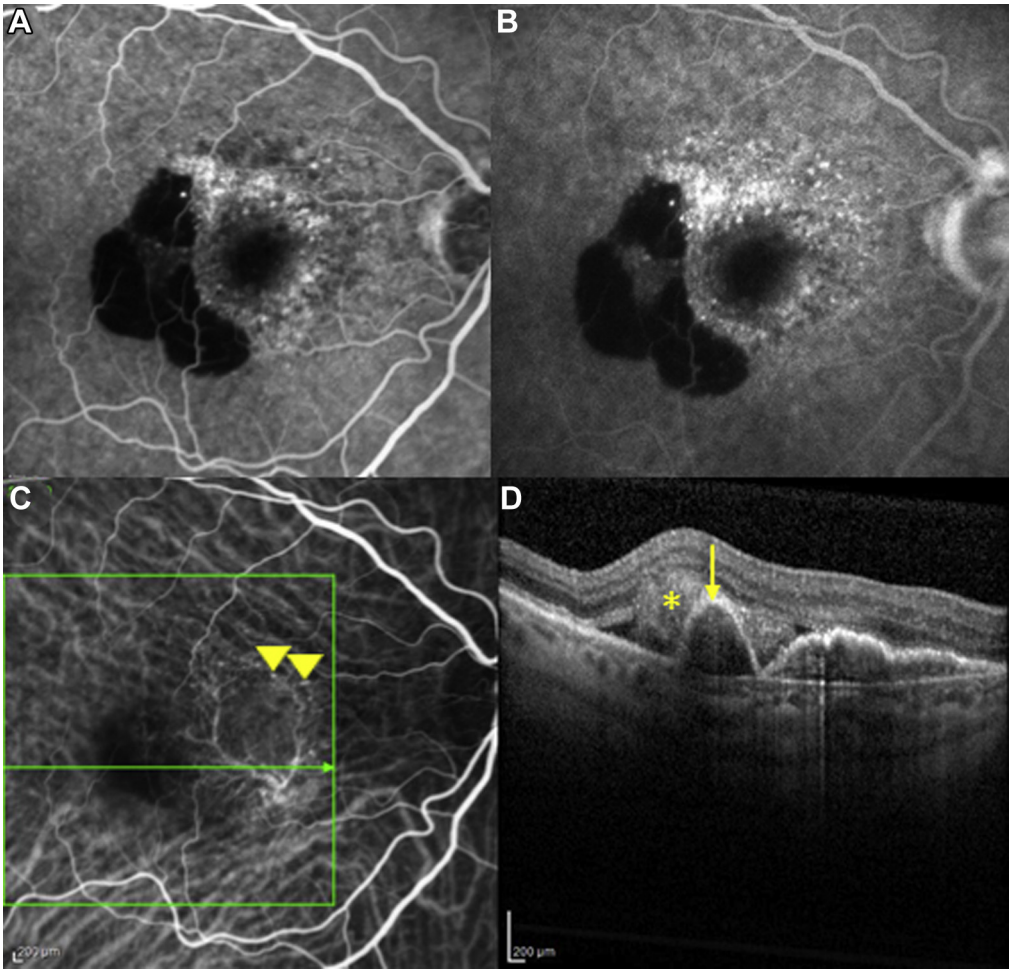

Figure 1. Polypoidal choroidal vasculopathy in a white woman. **A**, **B**, Early- and late-phase fluorescein angiograms, respectively, showing central and temporal retinal pigment epithelial detachment with subretinal hemorrhagic blocking defects. Note the superior occult leakage. **C**, Indocyanine green angiogram showing branching vascular networks with aneurysmal dilations (arrowheads) superiorly. **D**, B-scan OCT showing retinal pigment epithelial detachment (arrow) with subretinal hemorrhage visualized on OCT and subretinal hyperreflective material (asterisk).

between the prevalence of subretinal hemorrhage in eyes with or without PCV ($P = 0.299$).

Baseline SF was noted in 45.4% of eyes (98/216). Of the 98 eyes with SF at initial presentation, 78.6% (77/98 eyes) showed persistent SF after 4 injections and were classified into the anti-VEGF–resistant group. However, 21.4% of eyes (21/98 eyes) with initial SF showed resolution after 4 injections and were classified in the anti-VEGF–sensitive group. Baseline macular edema was noted in 47.2% of eyes (102/216 eyes). Of the 102 eyes with macular edema at presentation, 55.8% (67/120 eyes) showed persistent macular edema after 4 injections and were classified into the anti-VEGF–resistant group. Macular edema resolved after 4 injections in 34.3% of eyes (35/102 eyes), and these were classified in the anti-VEGF–sensitive group.

Discussion

Anti-VEGF therapy has become the standard treatment for exudative AMD, but continued leaking and bleeding despite initial treatment occurs in a significant number of eyes. These patients with continued leakage and bleeding also tend to show a worse visual prognosis. Indocyanine green angiography was not used in the evaluation of exudative AMD in major clinical trials[1–3] and is critical in making a definitive diagnosis of PCV.[6] Because of this, the potential effect of the presence of PCV on treatment response is unknown. Case series have shown that PCV may be more common in anti-VEGF–resistant eyes.[10,11] This study showed that the prevalence of PCV is significantly higher in anti-VEGF–resistant eyes than in anti-VEGF–sensitive eyes (50% vs. 30.2%; $P < 0.001$). These data support that diagnostic techniques to detect PCV in eyes with exudative AMD at presentation could be useful to clinicians, because PCV or subretinal aneurysmal neovascularization could be predictive of increased anti-VEGF resistance.

Polypoidal choroidal vasculopathy is an important subtype of exudative AMD characterized by polypoidal or aneurysmal dilation(s) with or without a BVN usually located beneath the RPE (type I choroidal neovascularization).[7] In the

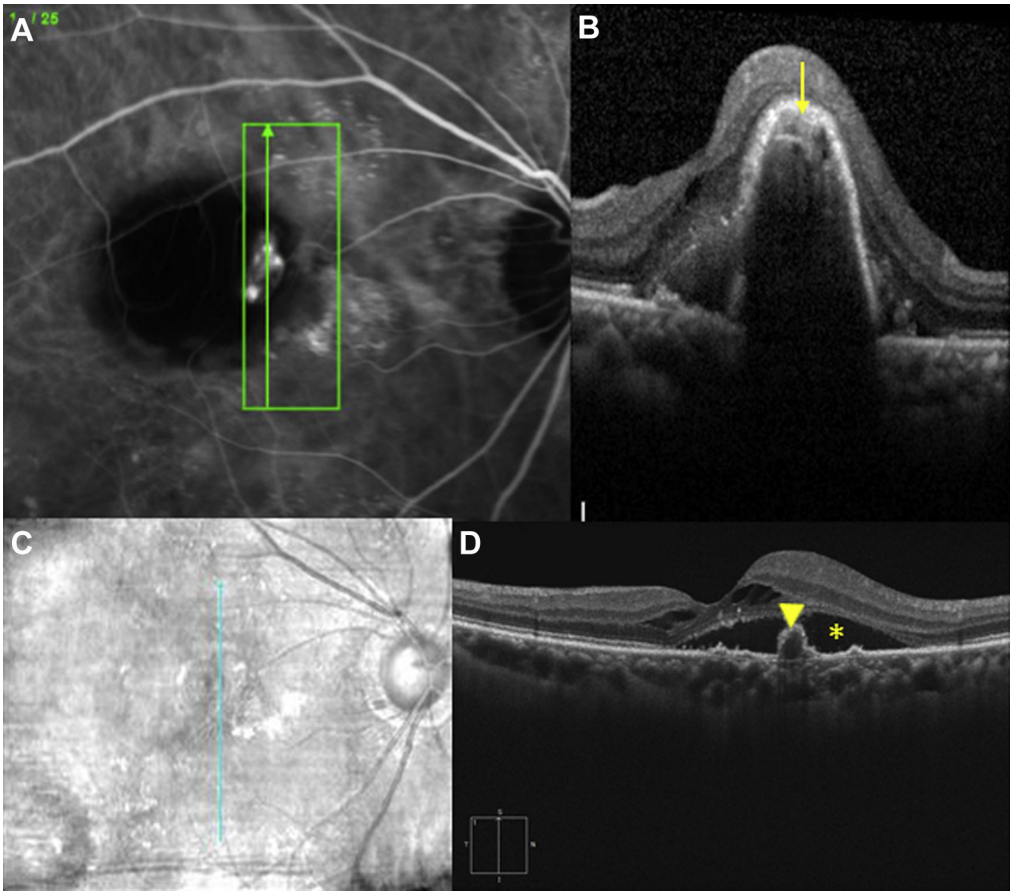

Figure 2. Anti–vascular endothelial growth factor (VEGF) resistance in an Asian woman diagnosed with polypoidal choroidal vasculopathy. **A**, **B**, Baseline indocyanine green angiograms showing polypoidal lesion with pigment epithelial detachment (arrow) on corresponding B scan. **C**, **D**. Vertical line OCT images showing persistent polypoidal lesion (arrowhead) and subretinal fluid (asterisk) after 4 anti-VEGF therapy injections.

overall demographic, eyes diagnosed with PCV on ICGA were more likely to be treatment resistant (66.7% vs. 46.8%; $P < 0.001$) than eyes without PCV. The diagnosis was made best on evaluating the indocyanine green angiogram using the scanning laser ophthalmoscope at between 3 and 5 minutes after dye injection and then using multimethod correlation with the B-scan OCT findings.[7] On OCT, the polyps appear as inverted U-shaped elevations of the RPE with heterogeneous reflectivity, and the BVN appears as a shallow elevation of the RPE (double-line sign; Fig 1).[7]

The demographics of the patient population in Hawaii allow evaluation of the prevalence of PCV in different ethnic populations. The overall PCV prevalence in exudative AMD was 45.1% (114/253 eyes) in Hawaii. The prevalence of PCV in Asian patients was 51.6% (81/157 eyes), which is consistent with the high prevalence noted in Asian countries.[17] The prevalence of PCV in white patients was 31.9% (23/72 eyes). This is higher than generally recognized previously, but few other studies of PCV in white persons used the scanning laser ophthalmoscope for ICGA, which is much more sensitive in identifying PCV than fundus camera ICGA.[21–23] To our knowledge, this is the only study evaluating the diagnosis and prevalence of PCV in different ethnic populations using the same diagnostic criteria. One other study in white patients that did use the scanning laser ophthalmoscope with ICGA found a similar prevalence of PCV of 24.5% in patients with exudative AMD mostly of European ancestry in Brazil.[20] Interestingly, the female predominance of exudative AMD without PCV was confirmed overall and also was noted for both Asian and white patients. However, the male predominance noted in PCV also was confirmed overall and also was noted in both white and Asian patients.

Anti–vascular endothelial growth factor resistance was defined as persistent SF, macular edema, or subretinal hemorrhage after 4 sequential anti-VEGF injections (Fig 2), whereas anti-VEGF sensitivity was defined as the absence of subretinal blood, SF, or intraretinal fluid after 4 sequential anti-VEGF injections (Fig 3). Overall, the proportion of PCV in anti-VEGF–resistant eyes was 50%, which was significantly higher than the 30.2% prevalence of PCV noted in anti-VEGF–sensitive eyes. In the Asian patient population, there was higher PCV prevalence at 56.2% in the anti-VEGF–resistant group, which was significantly higher than the 37.1% in the anti-VEGF–sensitive group by a factor of 1.5. In the white patient population, there was a much higher prevalence of PCV at 43.2% in the

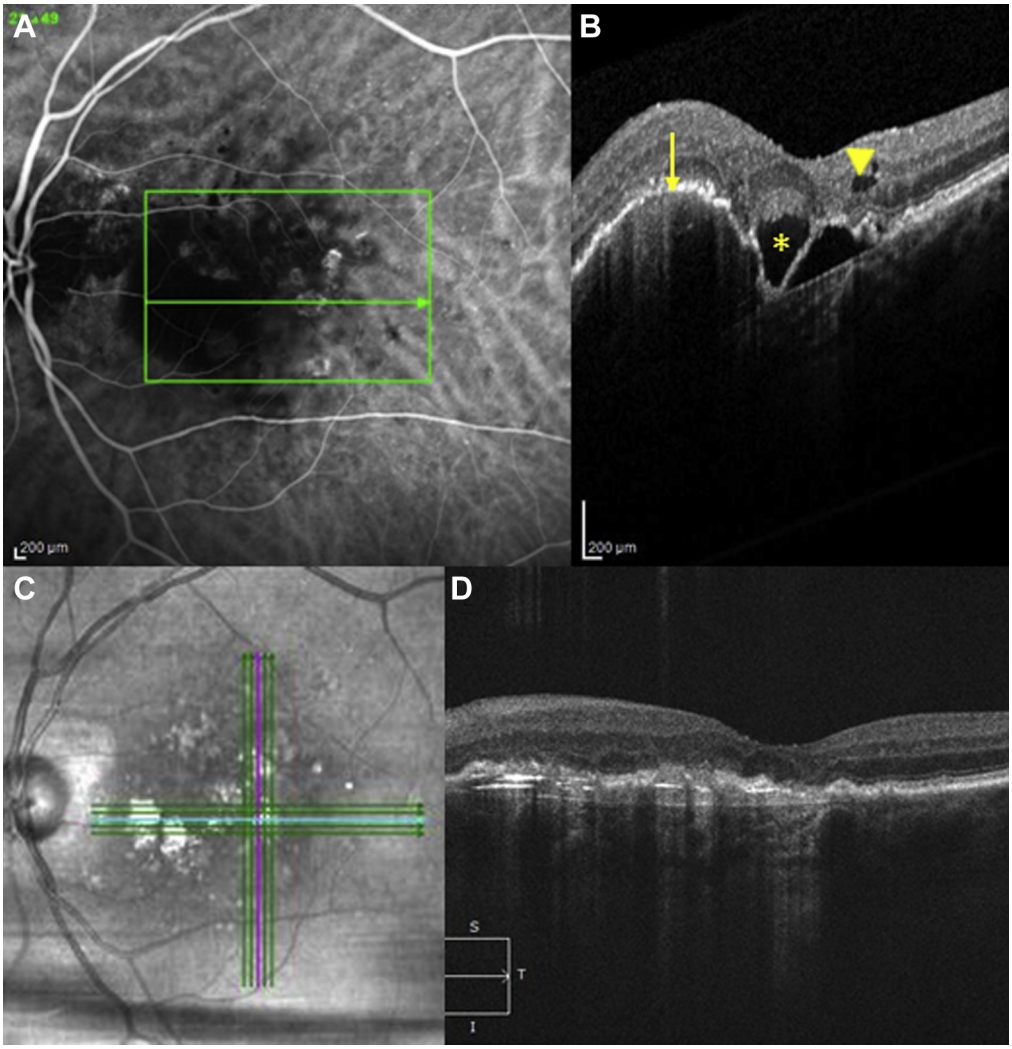

Figure 3. Anti–vascular endothelial growth factor (VEGF) sensitivity in a white woman with polypoidal choroidal vasculopathy. **A**, Baseline indocyanine green angiogram showing temporal polypoidal choroidal vasculopathy with central pigment epithelial detachment. **B**, Corresponding B-scan OCT showing hemorrhagic retinal pigment epithelial detachment (arrow) with subretinal fluid (SF; asterik) and macular cystic changes (arrowhead). **C**, **D**, OCT images obtained after 4 anti-VEGF injections. Note the resolution of the SF and retinal pigment epithelial detachment on OCT.

anti-VEGF–resistant group than the 16% in the anti-VEGF–sensitive group by a factor of 2.7. This indicates that PCV may be more important to diagnose in white patients because of the much higher prevalence of PCV in anti-VEGF–resistant eyes. The anti-VEGF resistance study performed in Switzerland showed a similar large ratio of the difference in PCV prevalence in anti-VEGF–resistant eyes versus anti-VEGF–sensitive eyes of 3.8 in white patients.[12] In this study, there was a significantly higher prevalence of PCV in anti-VEGF–resistant eyes in both white and Asian patients.

Treatment-resistant eyes also were more likely to be male, to be slightly younger, to have a history of smoking, and to have a larger initial CFT. These findings are interesting because smoking long has been associated with AMD and worse outcomes. In addition, eyes with higher CFT and more edema took longer to resolve. Because this study was performed in Hawaii with a unique demographic mix of Asian, white, and Pacific Islander patients, there was a higher proportion of Asian patients than in many other areas of the United States. Polypoidal choroidal vasculopathy in Asian eyes is more likely to be seen in men.[17] Previous initial reports of PCV in black and white patients show a female predominance.[15,16] In this study, in which more than 70% of our PCV population was Asian, anti-VEGF–resistant exudative AMD was more likely to be seen in male patients. Other study populations with a different ethnic mix may not show a male predominance. However, PCV was found to be more prevalent in males in both Asian and white patients in this current study.

This was a retrospective study, which has a number of limitations. Patients were treated with different anti-VEGF drugs. The groups sensitive and resistant to anti-VEGF therapy were equivalent with regard to percentage of eyes that were treated with aflibercept. However, the anti-VEGF–resistant group showed a statistically significant

larger proportion of eyes treated with bevacizumab, and the anti-VEGF−sensitive group showed a larger percentage of eyes treated with ranibizumab. However, this difference was likely to have a minimal impact on the results of the study. In prior major AMD trials, the 3 medications compared similarly in the first few months, the time frame applicable to this study. Bevacizumab was noninferior to ranibizumab in the Comparison of Age-Related Macular Degeneration Treatments Trials and IVAN trial.[8,24] In the VIEW 1 and VIEW 2 studies, monthly dosing of ranibizumab and aflibercept demonstrated comparable efficacy in the first 3 months.[3] Studies have shown that aflibercept may be superior to the other intravitreal anti-VEGF agents in eyes with the PCV variant. The EPIC trial showed that some PCV eyes resistant to the intravitreal anti-VEGF agents ranibizumab or bevacizumab may respond better to treatment with intravitreal aflibercept.[25] However, there was no statistically significant difference in percentage of eyes treated with aflibercept in the groups resistant and sensitive to anti-VEGF in the current study.

Another limitation of this study is the lack of a widely accepted definition of anti-VEGF resistance and anti-VEGF sensitivity. There is controversy regarding whether this should be based on visual or anatomic criteria. However, in a retrospective study, an anatomic definition is more widely applicable because there are not standardized Early Treatment Diabetic Retinopathy Study refractions available in a retrospective study. Disease activity was defined as persistent macular edema, SF, or subretinal hemorrhage after 4 injections. Four injections was chosen to allow for the full effect of the initial sequential treatment and to allow resolution of initial subretinal hemorrhage. Subretinal hemorrhage that is present after 4 injections was considered persistent disease activity. In the pro re nata study by Hatz and Prünte,[12] the authors also used subretinal hemorrhage as a criteria for disease activity. In clinical studies, this is also used as a criteria to continue treatment. In addition, subretinal hemorrhage is important to consider with regard to PCV, because a higher degree of subretinal hemorrhage may be seen associated with PCV.

Polypoidal choroidal vasculopathy is significantly more prevalent in anti-VEGF−resistant eyes. Although the prevalence of PCV varies in different ethnic backgrounds, PCV was found to be more prevalent in anti-VEGF−resistant eyes in both Asian and white patients. The subretinal aneurysmal neovascularization of PCV thus is an important phenotypic marker of anti-VEGF resistance in exudative AMD. Currently, ICGA using the scanning laser ophthalmoscope is the most sensitive way to make the diagnosis of PCV. Other noninvasive diagnostic testing methods are less sensitive but may prove helpful in making the diagnosis of PCV when ICGA is not available or when frequent follow-up diagnostic testing is being performed to observe treatment response. These methods include B-scan OCT, en face OCT, and OCT angiography.[26−29] The diagnosis of PCV may help to guide therapy in these anti-VEGF−resistant eyes. Alternative therapy may be considered, such as combination PDT and anti-VEGF injection, as recently supported by the EVEREST II trial.[14] This study confirmed the higher prevalence of PCV noted in Asian patients, but PCV prevalence was higher in white patients than recognized previously. Polypoidal choroidal vasculopathy is an important subtype of exudative AMD to diagnose, because it can be a clinically useful marker of anti-VEGF resistance, thereby helping to guide therapeutic decisions.

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **BVN** = branching vascular network; **CFT** = central foveal thickness; **ICGA** = indocyanine green angiography; **PCV** = polypoidal choroidal vasculopathy; **PDT** = photodynamic therapy; **RPE** = retinal pigment epithelium; **SF** = subretinal fluid; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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