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Comparison of Progression to Advanced Stage between Polypoidal Choroidal Vasculopathy and Age-Related Macular Degeneration in Korea

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Purpose: To compare the rate of progression to advanced stage in the fellow eye of patients with typical age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV) in a South Korean cohort.

Design: This is an observational, consecutive retrospective case series.

Participants: Patients with unilateral advanced stage AMD (n = 288; 180 typical AMD patients and 108 PCV patients).

Methods: Clinical assessment included detailed eye examination, including fundus photography, fluorescein angiography, and indocyanine green angiography.

Main Outcome Measures: Five-year progression rate to advanced stage in the fellow eye based on initial Age-Related Eye Disease Study (AREDS) score and the correlation between the initial AREDS score and progression to advanced disease in the fellow eye according to types of AMD.

Results: Five-year progression to advanced disease in the fellow eye was similar between typical AMD and PCV cases (11.1% vs. 14.8 %, respectively; $P = 0.466$, log-rank test). Among patients with initial AREDS score of 2 (normal macula or small drusen on the fellow eye), a higher proportion of patients progressed to advanced disease in the PCV group compared with typical AMD patients (10.4% vs. 2.4 %, respectively; $P = 0.0042$, log-rank test). Initial AREDS score correlated significantly with progression of the fellow eye to advanced stage in the typical AMD group, after adjusting for age, gender, and other comorbidities (hazard ratio [HR], 9.5; 95% confidence interval [CI], 2.80−32.12; $P = 0.0003$). However in the PCV group, initial AREDS score did not correlate with progression to advanced stage in the fellow eye (HR, 1.84; 95% CI, 0.83−4.05; $P = 0.13$).

Conclusions: Unlike typical AMD, PCV progresses without typical features such as drusen or pigmentary abnormality. Baseline AREDS score was less likely to predict progression of the fellow eye to advanced-stage disease in PCV compared with typical AMD. Therefore, the globally recognized risk-scoring AREDS system may not be applicable in Asia, where PCV is a prevalent subtype of AMD. *Ophthalmology Retina 2017;■:1−6 © 2017 by the American Academy of Ophthalmology*

Polypoidal choroidal vasculopathy (PCV) is recognized by orange nodules on fundus examination, polypoidal lesions on indocyanine green angiography, or both[1,2]; is seen more commonly among Asian and black persons; and now is thought to be a subtype of age-related macular degeneration (AMD).[3,4] Previous reports suggest that the clinical findings and natural history of PCV may differ from those of typical AMD. Iwama et al[5] report that drusen have only a minor effect on the clinical course of PCV, whereas Sasaki et al[6] report that there were differences in the fundus features that predict progression and development of advanced stage between typical AMD and PCV. Macular drusen are considered an important factor for predicting disease progression in AMD.[7−9] An international classification and grading system for AMD mainly emphasizes drusen size[10] and pigmentary abnormalities to determine the risk score for AMD progression, which could predict development of advanced AMD according to the Age-Related Eye Disease Study (AREDS). However, this classification and grading system was developed in a white population and has not been validated in an Asian population.

Therefore, the goal of this study was to compare clinical features related to the progression of disease between typical AMD and PCV in an Asian population using a simplified AREDS risk score system.[11] Based on our results, we question the appropriateness of the simplified AREDS risk score system when applied to the Asian population, in which PCV seems to be the predominant subtype of neovascular AMD.

Methods

We retrospectively reviewed medical records of 677 patients who visited the Vitreoretinal Service at Yonsei University Medical Center between April 1, 1991, and August 31, 2014. This

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Table 1. Baseline Characteristics of Unilateral Advanced Age-Related Macular Degeneration Patients versus Polypoidal Choroidal Vasculopathy Patients

	Typical Age-Related Macular Degeneration (n = 180)	Polypoidal Choroidal Vasculopathy (n = 108)	P Value*
Age (yrs), mean ± SD	69.8±7.3	65.6±8.0	<0.001
Gender (male:female)	80:100	65:43	0.011
Hypertension, no./ total no. (%)	61/180 (33.9)	25/108 (23.1)	0.063
Initial AREDS severity score, no./total no. (%)			0.01
2	83/180 (46.1)	67/108 (62.0)	
3	97/180 (53.9)	41/108 (38.0)	

AREDS = Age-Related Eye Disease Study; SD = standard deviation.
*Independent *t* test and chi-square test.

retrospective study was approved by the institutional review board of Yonsei University College of Medicine (reference no., 4-2015-0133) and was conducted in accordance with the tenets of the Declaration of Helsinki. Because this was a retrospective study, informed consent requirements were waived by the institutional review board. Inclusion criteria were: age 50 years or older, first diagnosis of unilateral advanced AMD or PCV, and follow-up period of at least 12 months. Exclusion criteria included concomitant diabetes mellitus, other retinal disease such choroidal neovascularization (secondary to myopia, ocular histoplasmosis syndrome, or angioid streak), central serous chorioretinopathy, vein or artery occlusion, or epiretinal membrane.

At the initial visit, all patients underwent a dilated fundus examination with an indirect ophthalmoscope, 30° colored fundus photography using the Heidelberg Retinal Angiography system (Heidelberg Engineering, Heidelberg, Germany), spectral-domain OCT (Cirrus OCT [Carl Zeiss, Berlin, Germany] or Spectralis OCT [Heidelberg Engineering]), digital fluorescence angiography, and indocyanine green angiography. During the follow-up period, color fundus photography and OCT were performed periodically. Data were collected from baseline to the end of the follow-up period for each patient.

Unilateral advanced AMD was defined as advanced AMD features in only 1 eye and no sign of advanced disease in the fellow eye. Advanced-stage AMD was defined as fibrovascular or hemorrhagic pigment epithelial detachment, subretinal or sub−retinal pigment epithelium hemorrhage, intraretinal hemorrhage or turbid exudate, subretinal fibrous scars, and geographic atrophy in the macula.[10] Geographic atrophy was diagnosed based on the presence of depigmentation of retinal pigment epithelium specified by the following 3 characteristics: roughly round or oval shape, sharp margins, and visibility of underlying large choroidal vessels in the central 3000 μm, with drusen or pigmentary abnormalities without neovascular features.[12] The diagnosis of PCV was made when subretinal hemorrhage, pigment epithelial detachment, and subretinal fluid associated with orange nodules on fundus photographs were present with polyps or a branching vascular network visible on indocyanine green angiography using the Heidelberg Retinal Angiography system (Heidelberg Engineering) equipped with a confocal scanning laser ophthalmoscope.

Grading of Age-Related Macular Degeneration According to Age-Related Eye Disease Study Score

We evaluated the initial fundus photographs from unilateral advanced AMD patients to assign AREDS scores using the simplified 5-step severity scale involving drusen size and pigmentary abnormalities.[11] Initial fundus findings were categorized as normal macula, small drusen (less than 63 μm in diameter), intermediate drusen (diameter between 63 and 125 μm), large drusen (more than 125 μm in diameter), or pigmentary abnormality. The severity scale system assigned 2 points for preexisting advanced AMD, 1 point for large drusen on either eye, 1 point for intermediate drusen on both eyes, 1 point for pigmentary abnormality on either eye, and 0 points for normal macula or presence of small drusen. All participants enrolled in the current study had advanced AMD in 1 eye, so the AREDS score was 2 or more. If the fellow eye had large drusen or pigmentary abnormality, the score was 3. If a patient had large drusen and pigmentary abnormality in the fellow eye, the score was 4.

The primary retinal specialist initially read the fundus photograph according to the AREDS criteria, and this result was compared with results from a masked grader (Y.S.). For the cases with inconsistent grading, the decision for final AREDS score was made by a third grader (H.J.K.). Based on the initial AREDS severity scale, the rate of progression to advanced-stage disease in the fellow eye was calculated for every unilateral case of advanced typical AMD and PCV.

Statistical Analysis

The independent-sample *t* test for continuous variables and chi-square test for nominal variables were used to compare baseline characteristics. The primary end point was the presence of advanced-stage disease in the fellow eye at any of the follow-ups. Main exposure of interest was the initial AREDS score. Gender, age, hypertension status, and type of AMD were adjusted in multivariate analysis. Kaplan-Meier survival analysis was used to evaluate the 5-year progression rate to advanced stage in the fellow eye. The Cox proportional hazard regression model was used to evaluate the univariate and multivariate risk of progression to advanced AMD in the fellow eye. To understand the interrelationship between initial AREDS scoring and progression to advanced stage disease according to the type of AMD (typical AMD vs. PCV) in the fellow eye, the significance of multiplicative interaction terms (the type of AMD vs. initial AREDS score) was tested. Then, subgroup analysis was performed in typical AMD and PCV separately. SAS software version 9.4 (SAS Institute, Cary, NC) was used for all statistical analysis, and Stata software version 14.2 (Stata Corp, College Station, TX) was used to create the Kaplan-Meier survival graph. The threshold for statistical significance was considered to be $P < 0.05$.

Results

Among the 677 AMD patients with follow-up of at least 1 year, 389 patients were excluded according to the exclusion criteria. A total of 114 patients (29.3%) demonstrated bilateral advanced AMD, 168 patients (43.2%) demonstrated early AMD in both eyes, and 87 patients (22.4%) demonstrated other macular disease and 20 patients (5.1%) with diabetes mellitus, leaving 288 patients. Mean age was 68.2±7.8 years, with 145 men and 143 women. Mean follow-up duration was 73.3±48.7 months since the initial diagnosis of AMD.

Baseline characteristics of unilateral advanced AMD are shown in Table 1. There were 180 patients in the typical AMD group and 108 patients in the PCV group. Mean age was significantly younger (69.8 vs. 65.6 years; $P < 0.001$, independent-sample *t* test), with more men (44.4% vs. 60.2%; $P = 0.011$, chi-square