TABLE 4. Associations of the Four Single Nucleotide Polymorphisms with Choroidal Neovascularization Development in Highly Myopic Eyes

	15q14						15q25					
	rs634990 C			rs524952 A			rs8027411 T			rs17175798 C		
	Frq	OR (95% CI)	P*	Frq	OR (95% CI)	P*	Frq	OR (95% CI)	P*	Frq	OR (95% CI)	P*
High myopia with no CNV (n = 600)	0.53			0.53			0.61			0.61		
High myopia with CNV (n = 450)	0.51	0.93 (0.78–1.11)	0.41	0.51	0.93 (0.78–1.10)	0.38	0.62	1.04 (0.87–1.25)	0.64	0.60	0.95 (0.79–1.13)	0.54

Frq, allele frequency.
* Age and sex adjustment was performed based on a logistic regression model.

without CNV to check for a possible difference between these two groups in the genetic background of the four myopia-susceptibility variants. Distributions of these four genotypes were all in HWE ($P > 0.2$), and there was no significant difference in the allele frequencies of SNPs between high myopia with CNV and high myopia without CNV—even after age and sex adjustment.

The average age was 54.9 ± 14.9 years in the patients without CNV, while the average age was 60.7 ± 13.3 years in the patients with CNV ($P < 0.0001$). Because the average age was significantly higher in the group with CNV, we performed subanalysis dividing the cohort into 40- to 49-year-old, 50- to 59-year-old, 60- to 69-year-old, and 70- to 79-year-old subgroups (Table 5). Our subanalysis revealed that there were no associations between CNV occurrence and the genotype variation in rs634990, rs524952, rs8027411, and rs17175798.

DISCUSSION

Myopia has been thought to be a multifactorial disease, and for more than a decade many researchers have sought the susceptibility genes associated with myopia. Several chromosome loci have been reported to be associated with common myopia, high myopia, or both[16–31]; however, some other investigators could not replicate these associations.[32–34] To date, no genes have been identified that are consistently responsible for either common or high myopia. Furthermore, it has not been clear if common and high myopia share the same genetic background or if high myopia has a unique genetic background that distinguishes it from common myopia. In the present study, we have shown that SNPs in 15q14 are associated significantly with high myopia in Japanese and that SNPs in 15q25 might also be associated. These same SNPs have been reported recently to be associated with myopia in Caucasians,[46,47] although the Caucasian cohort was population-based and patients with high myopia were extremely rare (1.7%–4.0%). Common and high myopia may well share the same genetic background—at least in part.

In the present study, we used two distinct control groups: cataract patients with axial lengths <25.00 mm in both eyes (control group 1, n = 366) and representative of the general Japanese population (control group 2, n = 929). Because control group 2 is representative of the general Japanese population, high myopia patients may well be included as control subjects. When one considers the high rate of high myopia in Japanese compared to Caucasians, in whom it is estimated to be present in approximately 5% of the general population, this could weaken the detection of any genetic association with high myopia. However, we believe that using the general population as a control is certainly acceptable for a case control study of high myopia.[44]

When evaluated with both controls, 15q14 showed a significant association with high myopia. The odds ratio of rs634990 CC genotype to TT genotype was 1.65 (95% CI, 1.19–2.29) when compared with control group 1 and 1.84 (95% CI, 1.44–2.36) when compared with control group 2, findings that are compatible with the reported odds ratio of 1.83 (1.42–2.36) for refractive error and myopia in a general population of Caucasians. The genetic variation at 15q14 seems to contribute to common myopia and to high myopia in a similar manner.

With 15q25, however, the association significance was only marginal when evaluated with control group 2, and the analysis with control group 1 showed no association to high myopia. In accordance with the original report, the risk allele was T in rs8027411. Because control group 2 consisted of the general population, and because patients with high myopia may be included as control subjects, this could lower the power of this study to detect a genetic association with high myopia. However, two SNPs in 15q25 were significantly associated with high myopia evaluated with control group 2. Considering that the minor allele frequencies in 15q25 were very similar be-

TABLE 5. Subanalysis of the Associations of the Four Single Nucleotide Polymorphisms with Choroidal Neovascularization Development in Highly Myopic Eyes

	n		P Value*			
Age, y	High Myopia with CNV	High Myopia with No CNV	rs634990	rs524952	rs8027411	rs17175798
<40	37	99	0.55	0.42	0.63	0.63
40–49	47	92	0.13	0.14	0.18	0.28
50–59	91	143	0.88	0.89	0.74	0.79
60–69	145	149	0.79	0.73	0.98	0.66
70–79	103	84	0.91	0.90	0.48	0.61
≥80	27	33	0.58	0.61	0.54	0.65

tween our control groups 1 (n = 366) and 2 (n = 929) and the original study showed that the odds ratio was very low as 1.16 (1.02–1.28) for the rs8027411 T allele, the size of control group 1 might be insufficient to detect the association. Even for the analysis with control group 2, the association becomes negative after Bonferroni correction. We might have to negate the association of 15q25 locus. Although our present study could be regarded as a replication study for the association of previously reported loci to myopia, and because the Bonferroni correction might not be applicable for a replication study, we would have to interpret the association of 15q25 locus in the present study with caution. Because the association of 15q25 to myopia was reported to be very low and the minor allele frequencies in 15q25 were very similar between control groups 1 and 2, additional study with a larger cohort might reveal the true association of 15q25 to myopia.

We also evaluated the genetic difference between high myopia patients with CNV and high myopia patients without CNV, and found that the genotype distribution of the SNPs evaluated was not significantly different. These high myopia patients without CNV might develop CNV later. Because CNV will develop only in 5% to 10% of high myopia patients and because it typically starts to develop in the fourth or fifth decades of life, the number of patients who will develop CNV later in these groups would be limited. However, the individuals who will develop CNV later in the control cohort would weaken the power to detect the associations to CNV development. Our negative result might be partly related to this weakened power. To eliminate the influence of such individuals, we performed subanalysis dividing the cohort into 40- to 49-year-old, 50- to 59-year-old, 60- to 69-year-old, and 70- to 79-year-old subgroups. Our subanalysis showed no associations of these loci to the CNV development. Although our findings should be interpreted with caution, factors other than 15q14 and 15q25 might affect the development of CNV in highly myopic eyes. Lacquer cracks and peripapillary atrophy can be the basis of CNV development. Although lacquer cracks and peripapillary atrophy do not always lead to CNV development, genomic studies paying attention to these features might give us loci associated with CNV development. The occurrence of CNV beneath the fovea is one of the most vision-threatening complications of highly myopic eyes, so it is important to study the mechanisms of CNV occurrence in such eyes even after susceptibility genes for myopia are known.

Because genetic associations have ethnic differences, our findings could not be compared directly to the previous studies that were performed in Caucasians. Furthermore, these previous reports of associations of 15q14 and 15q25 with myopia used a general population, while we performed a case control study using high myopia patients as the cases and the general population as controls, so our control cohort is almost the same as the entire cohort used in the previous studies. Although the associations of 15q14 and 15q25 to refractive error (myopia) and/or high myopia need to be evaluated in various ethnicities, our findings of similar contribution of these loci to common myopia in Caucasians and to high myopia in Japanese suggests that 15q14 and 15q25 contribute to these two conditions in a similar manner, although additional studies might reveal genetic differences that differentiate high myopia from common myopia. Moreover, additional genetic background might also affect the occurrence of myopia/high myopia, given at most 30% of PAR.

In conclusion, we have shown that genetic variations at 15q14 are associated significantly with high myopia in Japanese. Based on our findings and those of previous studies, this might be a susceptibility locus for both myopia and high myopia. The association of 15q25 should be evaluated in additional studies with larger cohorts. Our findings also suggest that CNV occurs independent of genetic variations at these loci, and that other factors affect the occurrence of CNV in highly myopic eyes.

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CLINICAL STUDY

Prognostic factors for visual outcomes 2-years after intravitreal bevacizumab for myopic choroidal neovascularization

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Abstract

Purpose **To determine the pre-treatment ocular factors significantly associated with the visual outcome 24 months after intravitreal bevacizumab (IVB) for myopic choroidal neovascularization (mCNV).**

Methods **A total of 23 eyes of 23 patients with mCNV were treated with IVB followed by as needed therapy. The efficacy of IVB was evaluated by the best-corrected visual acuity (BCVA) at 24 months after the initial treatment. Forward stepwise multiple linear regression analyses were performed to evaluate the influence of pre-treatment factors on the BCVA and the improvement of the BCVA at 24 months.**

Results **The mean pre-IVB BCVA was 0.74 ± 0.30 logarithm of the minimum angle of resolution (logMAR) units, and it improved to 0.43 ± 0.31 logMAR units after 1 month ($P<0.001$, paired *t*-test). The improvement was maintained at 24 months (0.46 ± 0.40, $P<0.005$). The mean number of IVB performed during the 24 months was 1.35 ± 0.71. Forward stepwise regression analysis showed that the pre-IVB CNV size (standardized $\beta=0.52$, $P<0.01$) and BCVA (standardized $\beta=-0.44$, $P<0.05$) significantly affected the visual acuity change after 24 months. The CNV size was the only factor that significantly affected the BCVA after 24 months (standardized $\beta=0.56$, $P<0.01$).**

Conclusions **IVB with as needed therapy for mCNV led to a rapid and sustained visual improvement. Smaller CNV size was a significant prognostic factor that predicts better visual acuity. Patients with lower pre-treatment BCVA had better visual recovery than those with better pre-treatment BCVA, however, this may be due to a ceiling/floor effect.**

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Keywords: myopic choroidal neovascularization; bevacizumab; prognostic factor; intravitreal injection

Introduction

Choroidal neovascularization (CNV) is a vision-threatening complication in eyes with pathological myopia. Myopic choroidal neovascularizations (mCNVs) have been shown to develop in 5 to 10% of eyes with pathological myopia,[1–3] and several studies have shown that mCNVs have a poor natural history.[4–6] For example, the visual acuity at 5 years after the onset of CNV decreased to ≤20/200 in 89% of the eyes and in 96% of the eyes after 10 years.[6]

Because of the poor natural history of mCNVs, several procedures have been tried to treat mCNVs, for example, thermal laser photocoagulation,[7] photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Pharma AG, Basel, Switzerland),[8] and intravitreal bevacizumab (Avastin; Genentech, South San Francisco, CA, USA), a recombinant humanized monoclonal anti-VEGF antibody. Earlier case series have reported good visual outcomes 1 to 2 years after intravitreal bevacizumab (IVB),[9–21] and at present IVB would be the first-line therapy for sub- and juxtafoveal mCNVs.[22] However, there is still not enough information to predict the visual outcome of each patient with mCNV treated with IVB.

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Thus, the purpose of this study was to determine the long-term visual outcome of IVB in eyes with mCNVs. We also determined which pre-IVB factors were significantly associated with the visual outcome 2-years after the IVB therapy.

Patients and methods

All of the procedures used in this study were approved by the Institutional Review Board at Kyoto University Graduate School of Medicine, and they conformed to the tenets of the Declaration of Helsinki. A written informed consent was obtained from each patient.

In this nonrandomized, non-comparative case series, we reviewed the medical records of patients with myopic CNV who were treated with IVB at the Kyoto University Hospital between 1 December 2006 and 31 December 2007. Before the IVB, all of the patients received a comprehensive ophthalmological examination, including best-corrected visual acuity (BCVA), intraocular pressure measurements, indirect ophthalmoscopy, slit-lamp biomicroscopy with a contact lens, fundus photography, optical coherence tomography (OCT), and fluorescein/indocyanine green angiography (FA/IA) using a confocal laser scanning system (HRA-2; Heidelberg Engineering, Heidelberg, Germany). The Stratus OCT3000 (Carl Zeiss, Dublin, CA, USA) or the OCT ophthalmoscope C7 (Nidek, Gamagori, Japan) examination of cross-sections (5–6 mm in length) centered on the fovea and on the mCNV were performed at the baseline examination. The size of the mCNV before treatment was measured on the FA/IA images using the embedded software programs in the HRA-2. The BCVA was measured with a Landolt chart, and the decimal values were converted to the logarithm of the minimal angle of resolution (logMAR) units.

The inclusion criteria were: (1) an axial length of $\geq$26.50 mm or spherical equivalent refractive error of ≥ -6.0 diopters (D) in phakic eyes; (2) fundus changes typical of pathological myopia, such as chorioretinal atrophy, lacquer cracks, or atrophic patches; (3) FA documentation of subfoveal or juxtafoveal CNV that showed active leakage; and (4) BCVA of $\geq$1.3 logMAR units (0.05 decimal units, 10/200 in Snellen acuity). The exclusion criteria were: (1) history of intraocular surgery except for cataract surgery; (2) previous treatment for the mCNV; and (3) other ocular disease that can influence the BCVA, such as corneal opacity or myopic foveoschisis. In patients who had undergone IVB in both eyes, the data from the right eye was used for the statistical analyses.

All patients who had a recent visual disturbance due to active subfoveal or juxtafoveal mCNV were offered the IVB treatment with an explanation of possible complications. The intravitreal dose of bevacizumab was 1.25 mg per 0.05 ml. All injections were performed in a sterile manner, and prophylactic topical antibiotics were applied from a few days before to 1 week after the injection. After the initial IVB, the BCVA was measured, indirect ophthalmoscopy, slit-lamp biomicroscopy, and OCT examination of cross-sectional images centered on the fovea and on the mCNV was performed at each visit, and additional examinations such as angiography were performed as needed. Retreatment with IVB was performed if the evaluating clinician judged a re-injection was needed. The re-injection criteria were any of following finding with visual loss at least 1 month after the previous IVB: (1) persistence or recurrence of macular edema and/or serous retinal detachment in the OCT images; (2) persistence or recurrence of dye leakage in the FA images; and (3) new subretinal hemorrhage from the mCNV.

The efficacy of IVB for mCNV was based on the BCVA measured at 1, 3, 6, 12, 18, and 24 months after the initial IVB. In addition, the change in the BCVA, number of IVBs, and number of serious complications during the 24 months follow-up were evaluated.

Paired *t*-tests were used to evaluate the significance of differences in the BCVA at two time points. Pearson's correlation analyses were used to assess the influence of each pre-treatment factor, viz, age in years, duration of symptom in months, axial length in mm, pre-treatment BCVA in logMAR units, pre-treatment CNV size in μm, and pre-treatment CNV location as subfoveal or juxtafoveal, on the BCVA change, and the BCVA at 24 months after the initial IVB. Stepwise forward multivariate linear regression analyses were also performed to evaluate the contribution of each pre-treatment factor to the BCVA change and the BCVA at 24 months after the initial IVB. These statistical analyses were performed using software R (http://www.r-project.org/). The pre-IVB location of the mCNV was given a numerical value of 1 for subfoveal mCNVs and 0 for juxtafoveal CNVs for the correlation and multiple regression analyses. Stepwise forward regression analyses were performed using the software R package 'maSigPro' (http://bioconductor.org/packages/release/bioc/html/maSigPro.html). All continuous values are presented as means $\pm$ SD. The level of statistical significance was set at $P<0.05$.

Results

A total of 28 eyes of 28 patients met the inclusion criteria. Of these 28 eyes, one eye showed severe inflammation with dense vitreous opacity 1 day after the fifth IVB and underwent pars plana vitrectomy.[23] We excluded this eye from the statistical analyses. There were no other severe

ocular or systemic adverse effects after the IVB. Of the remaining 27 eyes, four eyes of four patients were lost to follow-up 6 to 18 months after the initial treatment. Then the final number of eyes analyzed was 23 eyes of 23 patients.

The demographics of the 23 eyes of 23 patients are shown in Table 1. The mean age of the 23 patients (7 men and 16 women) at the time of the initial IVB was 65.1 ± 10.2 years with a range of 39 to 81 years. The mean axial length was 28.94 ± 1.70 mm with a range of 26.50 to 32.63 mm. All of the 23 CNVs were predominantly classic on FA, and the CNV was subfoveal in 14 eyes (60.9%) and juxtafoveal in 9 eyes (39.1%). The mean size of the CNV before treatment was 1803 ± 725 μm with a range of 750 to 3750 μm. The duration of the symptoms was 3.5 ± 2.2 months with a range of 1.0 to 8.5 months.

The mean BCVA before and 1, 3, 6, 12, 18, and 24 months after the initial treatment are shown in Figure 1. The mean pre-IVB BCVA was 0.74 ± 0.30 logMAR units with a range of 0.22 to 1.30 logMAR units. At 1 month after the initial IVB, the mean BCVA improved significantly to 0.43 ± 0.31 logMAR units ($P<0.001$; paired t-test). The improved BCVA was maintained at 0.46 ± 0.40 logMAR units 24 months after the first treatment ($P<0.005$). The BCVA in logMAR units was inversely proportional to decimal BCVA, and thus negative values of the mean BCVA change of the 23 eyes was −0.28 ± 0.40 logMAR units, which indicated that the mean BCVA had improved 24 months after the initial IVB. Of the 23 eyes, 14 eyes (60.9%) showed a visual improvement of 4 0.2 logMAR units at 24 months after the first treatment, and two eyes (8.7%) showed a visual loss of 4 0.2 logMAR units at 24 months after the first treatment. The mean number of IVB injections performed during the 24 months was 1.35 ± 0.71; 17 eyes (73.9%) had IVB only once; 5 eyes (21.7 %) had IVB twice; and 1 eye (4.4%) required four IVB injections.

We next evaluated whether significant correlations existed between pre-treatment factors and the change in the BCVA at 24 months after the initial IVB (Table 2). Pearson's correlation analyses showed that among the pre-treatment factors, the pre-treatment CNV size ($r=0.45$, $P<0.05$) and duration of symptoms ($r=0.42$, $P<0.05$) were positively correlated with the change in the BCVA at 24 months. These results suggested that smaller CNVs and shorter durations of symptoms before the IVB were significantly associated with a greater improvement of the BCVA at 24 months after the initial IVB therapy. The pre-treatment BCVA showed marginally but not significant correlation with the change in the BCVA at 24 months ($r=-0.37$, $P=0.087$). The pre-treatment CNV location ($P=0.27$), age ($P=0.70$), and axial length ($P=0.93$) were not significantly correlated with the change in the BCVA.

Forward stepwise multiple linear regression analysis with the visual acuity change at 24 months as the dependent variable showed that pre-treatment CNV size (standardized β (multiple regression coefficient) = 0.52, $P<0.01$) and pre-treatment BCVA (standardized $\beta=-0.44$, $P<0.05$) were significant contributing determinants. The duration of symptoms was not included in the stepwise selection procedure. The adjusted R^2 (coefficient of multiple determination) of the final model was 0.333.

Table 1 Demographics and Ocular Characteristics of the Study Population

Category	*Subcategory*	*Value*
Number of patients (eye)		23 (23)
Age (year)	Mean ± SD	65.1 ± 10.2
	Median (range)	65 (39–81)
Gender, no (%)	Men	7 (30.4%)
	Women	16 (69.6%)
Axial length (mm)	Mean ± SD	28.94 ± 1.70
	Median (range)	28.90 (26.50–32.63)
Refraction of phakic eyes (diopter)[a]	Mean ± SD	−12.62 ± 3.47
	Median (range)	−13.06 (−6.85 to −19.50)
Duration of symptoms (month)	Mean ± SD	3.5 ± 2.2
	Median (range)	2.5 (1.0–8.5)
CNV size before treatment (μm)	Mean ± SD	1803 ± 725
	Median (range)	1700 (750–3750)
CNV location, no (%)	Subfoveal	14 (60.9%)
	Juxtafoveal	9 (39.1%)

Abbreviation: CNV, choroidal neovascularization.
[a]For the calculation, seven eyes (30.4%) that had undergone cataract surgery were excluded. None of the eyes had undergone corneal refractive surgery.

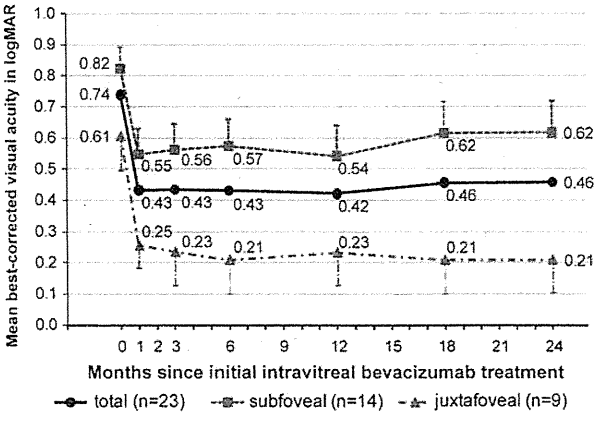

Figure 1 Changes of mean best-corrected visual acuity over 24 months after initial IVB therapy for a mCNV. The squares represent the results of subfoveal mCNVs ($n=14$), the triangles represent the juxtafoveal mCNVs ($n=9$), and the circles represent all of the eyes, that is, sum of the subfoveal and juxtafoveal mCNVs ($n=23$). Visual acuity was converted to a logarithm of the minimal angle of resolution (logMAR) units. The error-bar represents the SEMs.

Table 2 Correlation analysis and stepwise forward regression analysis to access the influence of each pre-treatment factor on LogMAR change at 24 months after initial IVB for mCNV

Covariate (Pre-treatment factors)	*Pearson's correlation analysis*		*Stepwise forward regression analysis*[a]	
	r	P-*value*	*Standardized* b	P-*value*
CNV size	0.45	0.032	0.52	0.0082
BCVA (logMAR)	−0.37	0.087	−0.44	0.020
Duration of symptoms	0.42	0.044	Not included	F
CNV location	0.24	0.27	Not included	F
Age	−0.08	0.70	Not included	F
Axial length	0.02	0.93	Not included	F

Abbreviations: BCVA, best-corrected visual acuity; logMAR, logarithm of the minimal angle of resolution; mCNV, myopic choroidal neovascularization; *r*, Pearson's correlation coefficient; *β*, regression coefficient.
[a]Adjusted R^2 (the coefficient of multiple determination) = 0.333.

Table 3 Correlation analysis and stepwise forward regression analysis to access the influence of each pre-treatment factor on BCVA in LogMAR at 24 Months after Initial IVB for mCNV

Covariate (Pre-treatment factors)	*Pearson's correlation analysis*		*Stepwise forward regression analysis*[a]	
	r	P-*value*	*Standardized* b	P-*value*
CNV size	0.56	0.0056	0.56	0.0056
CNV location	0.50	0.014	Not included	F
Duration of symptoms	0.49	0.019	Not included	F
BCVA in logMAR	0.39	0.065	Not included	F
Age	0.25	0.24	Not included	F
Axial length	−0.22	0.32	Not included	F

Abbreviations: BCVA, best-corrected visual acuity; logMAR, logarithm of the minimal angle of resolution; mCNV, myopic choroidal neovascularization; *r*, Pearson's correlation coefficient; *β*, regression coefficient.
[a]Adjusted R^2 (the coefficient of multiple determination) = 0.279.

We also evaluated the possible association of the pre-treatment factors with the BCVA at 24 months after the initial IVB treatment (Table 3). Pearson's correlation analyses showed that pre-treatment CNV size and pre-treatment CNV location were significantly associated with BCVA at 24 months ($r = 0.56$, $P < 0.01$ and $r = 0.50$, $P < 0.05$, respectively). The duration of the symptoms was also significantly correlated with the BCVA at 24 months ($r = 0.49$, $P < 0.05$). The pre-treatment BCVA showed marginally but not significant correlation ($r = 0.39$, $P = 0.065$) with BCVA at 24 months after initial treatment. Forward stepwise regression analysis showed that only the pre-treatment CNV size (standardized $\beta = 0.56$, $P < 0.01$) was included in the final model. The adjusted R^2 of the final model was 0.279.

Discussion

Although the dose of bevacizumab and follow-up strategy were different among the studies, earlier studies have reported that IVB for mCNV leads to a significant improvement in the BCVA with only a few injections. Thus IVB may be considered as first-line therapy for mCNV.[9–22] However, the follow-up periods were up to 1-year in most of the earlier studies. There have been a few studies that showed 2-years visual outcomes of IVB for mCNV, and the results have been conflicting.[9,18,20] Our results showed that IVB for 23 eyes with mCNV significantly improved the BCVA at 1 month (from 0.74 ± 0.30 logMAR units to 0.43 ± 0.31 logMAR units), and following an as needed strategy, the BCVA improvement was maintained over 24 months with 1.35 ± 0.71 times IVB. Baba *et al*[9] reported that 12 eyes with mCNV treated by 1.25 mg IVB had significant improvement of the BCVA from 0.75 ± 0.25 logMAR units at baseline to 0.50 ± 0.38 logMAR unit at 24 months after IVB, and mean number of injections was 1.6 ± 0.8 times. Ikuno *et al*[18] reported that 11 eyes with mCNV treated by 1.0 mg IVB showed significant improvement of the BCVA from 0.68 ± 0.29 logMAR units to 0.56 ± 0.31 logMAR unit at 1 month, and the improvement was maintained for 12 months. However, the significance of the improvement was not present at 18 and 24 months after the initial treatment, and the mean number of injections

was 2.9 ± 2.4 times. Voykov *et al*[20] reported that 11 eyes treated by 1.25 mg IVB monotherapy showed gradually improvements of the BCVA from 0.7 logMAR units to 0.5 logMAR unit with 2.2 times injections at 24 months after IVB, however, the improvement was marginally not significant.

There are several reasons for the differences of the results of these studies; for example, all four studies were retrospective, the sample sizes were relatively small, and there were differences of the baseline characteristics of the patients. Accumulation of the results of more studies, as well as prospective studies with a larger number of cohorts will be necessary to understand the long-term visual prognosis of IVB for mCNV. Several earlier studies also showed that IVB was more effective than photodynamic therapy for treating mCNV.[9,12,18,19,21] We could not compare the efficacy of IVB with the other treatments because our study was a non-comparative design.

The prognostic factor analyses showed that the pre-treatment CNV size was significantly associated with both the BCVA and the change in the BCVA at 24 months after the initial IVB. These results indicated that eyes with smaller mCNV had both better BCVA itself and better improvement of BCVA at 24 months after the initial IVB than those with larger mCNV. Our results showed that the mCNV size could be used as a prognostic factor for the BCVA after IVB for mCNV. Similar findings were reported for age-related macular degeneration (AMD) where the size of the CNV before PDT or anti-VEGF therapy was a predictive factor for the post-treatment BCVA.[8,24–28] However, the mechanism of how the CNV lesion size influences the visual outcome after these treatments has not been determined.

The pre-treatment BCVA was also significantly associated with the change in the post-IVB BCVA at 24 months, but it was not significantly associated with the BCVA itself at 24 months. Thus, patients with poorer BCVA acuity before treatment had greater recovery of the BCVA than those with better pre-treatment BVCA. Similar results were reported in subgroup analyses in the MARINA[25] and ANCHOR studies,[26] both of which were prospective, randomized, double-masked studies that evaluated effectiveness of another anti-VEGF drug, ranibizumab, for the treatment of AMD. In both subgroup analyses, better baseline BCVA, increasing age and larger CNV lesion size were associated with less improvement of the BCVA after the ranibizumab treatment. The authors suggested that the association between the baseline BCVA and the visual improvement after treatment was because patients with higher pre-treatment BCVAs had a smaller chance for improvement (ceiling effect), whereas patients with a greater impairment of the pre-treatment BCVA had a greater chance for improvement (floor effect).[25,26] We suggest that our results might also be due to the similar ceiling/floor effect, and we should not consider that IVB was less effective for the mCNV patients with better pre-treatment BCVA.

An earlier natural history study showed that eyes with juxtafoveal mCNV had better final BCVA than those with subfoveal mCNV.[5] The correlation analysis in our study showed that the pre-treatment location (subfoveal or juxtafoveal) of the mCNV was significantly correlated with BCVA at 24 months. However, the forward stepwise regression analysis did not show that the CNV location was a significant contributing determinant for the BCVA at 24 months. This might be partially because of the pre-treatment CNV location was correlated with the pre-treatment CNV size ($r = 0.45$, $P < 0.05$), that is, subfoveal mCNVs were larger than juxtafoveal mCNVs in this study. The duration of the symptoms was also correlated with pre-treatment CNV size ($r = 0.42$, $P < 0.05$). This might explain why the forward stepwise regression analysis did not include this covariant into the final models.

Although the patients' age has been shown to have influence on natural history and visual outcome after treatment of mCNVs,[24,29–32] it was not significantly associated with visual outcome after IVB treatment in our eyes. The reason might be that most of the patients in this study were older with a mean age of 65.1 ± 10.2 years, and 20 of the 23 patients (87.0%) were over 60 years of age. We could not assess the effectiveness of IVB for young patients with mCNV and additional study are needed to determine this.

The limitations of this study are its retrospective design and small sample size. The adjusted R^2 of the final regression models was 0.333 and 0.279, indicating that the revealed predictors leave a notable amount of variation of the dependent variables, that is, the BCVA and the change in the BCVA at 24 months. However, the results of this study showed that IVB followed by as needed strategy led to a rapid and significant visual recovery in patients with mCNV, and the visual recovery was maintained for 24 months after initial treatment. The pre-treatment CNV size was an important prognostic factor that was significantly associated with both the change in the BCVA and the BCVA at 24 months after initial treatment. The results indicated that patients with smaller pre-treatment mCNVs would have better visual recovery and better BCVA at 24 months after initial IVB. The patients with more impaired pre-treatment BCVA had better visual recovery than those with better pre-treatment BVCA, however, these results may be due to ceiling/floor effects.

Summary

What was known before

- IVB has been widely used to treat mCNV. Earlier studies reported good visual outcomes after 1 to 2 year follow-ups, however, there is still not enough information available that helps us to predict visual outcome for each patient.

What this study adds

- The results of our study showed that the CNV lesion size was a prognostic factor after IVB for mCNV; patients with smaller mCNVs had better visual recovery and BCVA at 24 months after initial IVB than those with larger mCNV. The results of our study also showed that patients with more impaired visual acuity before treatment got higher visual recovery, however, this might be due to ceiling/floor effect.

Conflict of interest

The authors declare no conflict of interest.

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CLINICAL STUDY

Development of polypoidal lesions in age-related macular degeneration

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Abstract

Purpose **To investigate the development of polypoidal lesions using indocyanine green angiography (IA) in eyes with typical age-related macular degeneration (AMD).**

Methods **We retrospectively reviewed the medical records of 47 consecutive patients (47 eyes) with typical AMD who had been followed up with IA for at least 2 years.**

Results **At the initial visit, although all eyes showed classic and/or occult choroidal neovascularization (CNV) associated with AMD, no eyes showed polypoidal lesions by IA. However, during follow-up, 13 (27.7%) of the 47 eyes did show polypoidal lesions. All polypoidal lesions developed at the edge of persistent CNV or, more often, at the terminus of recently progressed CNV. Of 12 eyes with a final lesion area >8 disc area, 7 (58.3%) showed newly developed polypoidal lesions. In the eyes with these newly developed polypoidal lesions, the mean area of the vascular lesion had extended significantly from $10.50 \pm 7.88\,mm^2$ to $20.87 \pm 10.21\,mm^2$ during follow-up ($P = 0.0018$).**

Conclusion **The current observation suggests that IA of active AMD sometimes reveals polypoidal lesions if there is progression of the CNV in the subretinal pigment epithelium space.**

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Keywords: age-related macular degeneration; indocyanine green angiography; polypoidal choroidal vasculopathy

Introduction

Initially, polypoidal choroidal vasculopathy (PCV) was described as a new clinical entity with a unique form of choroidal vascular abnormality.[1–3] As Uyama *et al*[4,5] proposed that PCV is a variant of choroidal neovascularization (CNV) in exudative age-related macular degeneration (AMD), it has been generally believed that the vascular components in PCV are a type of CNV, although the pathogenesis of PCV is not fully understood.[6,7] In general, PCV is diagnosed when polypoidal lesions are seen by indocyanine green angiography (IA) at the terminus of typical branching vascular networks.[8] IA is essential for the study of the vascular lesion of PCV because most of the vascular components of PCV are located beneath the retinal pigment epithelium;[8] hence, with fundus examination or fluorescein angiography (FA), it is often difficult to distinguish macular PCV from exudative AMD.[9–11]

An increasing number of reports has recently shown that anti-vascular endothelial growth factor (VEGF) therapy can reduce the exudative change and lesion size in exudative AMD, and can result in visual recovery.[12–18] However, some eyes with exudative AMD are refractory to repeated anti-VEGF therapy.[19,20] Clinicians sometimes see cases of typical AMD with a large lesion that shows a poor response to treatment and that shows progression, which results in a poor visual prognosis. When we performed IA on such AMD cases with large lesions, we sometimes noted knob-like hyperfluorescent lesions at the end of progressing CNV, which resembled the polypoid lesions typically seen in PCV.[21] Cho *et al*[19] reported that IA revealed these polypoidal lesions in 12 cases of exudative AMD with a poor response to anti-VEGF therapy.

In the clinical setting, FA is essential to make a diagnosis and to evaluate lesion size and its activity in exudative AMD.[22] Even in exudative AMD, IA often provides useful information about vascular lesions, especially those located beneath the retinal pigment

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epithelium.[23,24] So far, however, limited information is available using IA on long-term observations of the vascular components in typical AMD. In this study, we studied the vascular lesions of typical AMD using IA, to elucidate the rate and characteristics of eyes that were initially diagnosed as having typical AMD and that subsequently developed polypoidal lesions.

Patients and methods

For this observational case study, we retrospectively reviewed the medical records of 47 consecutive patients (47 eyes) with typical AMD who initially visited the Macula Service, Department of Ophthalmology, Kyoto University Hospital between October 2004 and October 2007 and whose eyes had been examined with both FA and IA for more than 2 years after the initial visit. During this period, 116 patients with typical AMD initially visited our clinic. In all, 69 patients were excluded from the current study because of a short follow-up period or because they lacked FA or IA during the more than 2 years since the initial visit. When both eyes showed typical AMD, only one eye was selected randomly for inclusion in the current study. This study was approved by the Institutional Review Board at the Kyoto University Graduate School of Medicine and adhered to the tenets of the Declaration of Helsinki.

The diagnosis of typical AMD was made based on fundus photographs, FA, IA, and optical coherence tomography (OCT), which showed type 1 and/or type 2 CNV. Eyes with other macular abnormalities (such as PCV, retinal angiomatous proliferation, pathological myopia, idiopathic CNV, presumed ocular histoplasmosis, angioid streaks, and other secondary CNV) were excluded from the current study. When reddish-orange nodules were seen by ophthalmoscopic examination or polypoidal lesions were seen by IA, the eye was excluded from the current study. Eyes that had been previously treated with focal laser photocoagulation, photodynamic therapy, vitrectomy, radiation therapy, or anti-VEGF therapy were also excluded from this study.

At the initial visit, all patients had undergone a comprehensive ophthalmological examination, including measurement of best-corrected visual acuity (VA), determination of intraocular pressure, indirect ophthalmoscopy, slitlamp biomicroscopy with a contact lens, and OCT. After fundus photographs were taken, FA and IA were performed on each patient using a confocal laser scanning system (HRA-2, Heidelberg Engineering, Dossenheim, Germany). VA measurement and OCT examination were performed on each patient at each follow-up visit; FA and IA were performed if necessary, and all patients in the current study were examined with both FA and IA several times during their follow-up.

In this study, the greatest linear dimension (GLD) and area of the lesion were determined based on the IA using software that was built into the HRA-2. GLD was defined as covering the entire CNV lesion, including type 1 and type 2 CNV, polypoidal lesions, and the branching vascular network. The area of the CNV lesion was measured manually using software in HRA-2. Pigment epithelial detachment, without underlying CNV, was not included in the measurement of GLD or in the area of the lesion. In the current study, one optic disc area (DA) is considered to be 2.54 mm^2 on the basis of one optic disc diameter being 1.8 mm.

Using OCT images, we performed two measurements using a caliper that was built into the software of the OCT machine; using these calipers, foveal thickness and thickness of the neurosensory retina in the fovea were measured. Foveal thickness was defined as the distance between the vitreoretinal interface and the retinal pigment epithelium; thickness of the neurosensory retina was defined as the distance between the vitreoretinal interface and the tip of the outer portion of the inner and outer segments of the photoreceptors.

In the current study, measurement values obtained at the initial visit were compared with those obtained at the final examination. To evaluate progression of the vascular lesions, the initial area of the CNV lesion and that of the GLD were compared with final values. To evaluate activity of the disease, we also compared the initial OCT measurement (foveal thickness and thickness of the neurosensory retina) with values obtained at the final visit. To compare the difference in VA, vision as measured with a Landolt chart was converted to a logarithm of the minimal angle of resolution (logMAR).

Statistical analysis was performed using software designed for this purpose (StatView, version 5.0; SAS Institute, Cary, NC, USA). A P-value <0.05 was considered to be statistically significant.

Results

In the current study, 47 eyes of 47 patients (36 men and 11 women) with typical AMD were examined; the patients ranged in age from 56 to 90 years (72.8 ± 7.5 years). The follow-up period ranged from 24 to 59 months (43.9 ± 10.3 months). All patients were examined with FA and IA repeatedly during their follow-up, ranging from 2 to 10 times (4.6 ± 1.8 times). Table 1 shows characteristics of patients who were eligible for this study. Mean baseline VA (logMAR) was 0.70 ± 0.53, and the mean initial areas of the lesion and GLD were

Table 1 Characteristics of patients with typical age-related macular degeneration

	Total (n = 47)	*Polypoidal lesion (+)* (n = 13)	*Polypoidal lesion (−)* (n = 34)	P-*value*
Gender (female/male)	11/36	3/10	8/26	0.9739
Age (years)	72.8 ± 7.5	73.1 ± 5.0	72.8 ± 7.5	0.8913
Initial conditions				
FA findings (predominantly classic/minimally classic/occult)	13/16/18	3/3/7	10/13/11	0.3857
Best-corrected VA (logMAR)	0.70 ± 0.53	0.64 ± 0.53	0.72 ± 0.53	0.6234
Area of lesion (mm^2)	8.68 ± 7.75	10.50 ± 7.88	7.99 ± 7.75	0.3262
GLD (mm)	3850 ± 1627	4231 ± 1692	3705 ± 1627	0.3269
Foveal thickness (mm)	523.8 ± 288.6	567.5 ± 427.9	507.1 ± 288.6	0.5269
Thickness of neurosensory retina in the fovea (mm)	284.8 ± 199.5	314.2 ± 317.6	273.6 ± 199.5	0.5388
Follow-up duration (months)	43.9 ± 10.3	47.4 ± 9.1	42.5 ± 10.3	0.1481
Treatment				
Photodynamic therapy	35	8	27	0.2087
(Number of treatments)	2.0 ± 1.1	2.4 ± 1.4	1.9 ± 1.1	0.3044
Anti-VEGF therapy	21	5	16	0.5959
(Number of treatments)	3.1 ± 4.1	3.0 ± 2.9	3.2 ± 4.1	0.9322
Final conditions				
Best-corrected VA (logMAR)	0.89 ± 0.50	0.74 ± 0.40	0.94 ± 0.50	0.2303
Area of lesion (mm^2)	14.28 ± 10.57	20.87 ± 10.21	11.77 ± 10.57	0.0068
GLD (mm)	4628 ± 1893	5880 ± 1947	4149 ± 1893	0.0039
Foveal thickness (mm)	449.4 ± 352.8	467.7 ± 334.0	442.5 ± 352.8	0.8292
Thickness of neurosensory retina in the fovea (mm)	245.0 ± 236.9	194.3 ± 127.6	264.4 ± 236.9	0.3700
Changes during follow-up				
Best-corrected VA (logMAR)	0.19 ± 0.45	0.11 ± 0.52	0.22 ± 0.45	0.4470
Area of lesion (mm^2)	5.60 ± 7.17	10.38 ± 9.35	3.78 ± 7.17	0.0036
GLD (mm)	777 ± 1306	1649 ± 1623	444 ± 1306	0.0035
Foveal thickness (mm)	−76.8 ± 364.6	−111.3 ± 463.5	−64.6 ± 364.6	0.7076
Thickness of neurosensory retina in the fovea (mm)	−38.5 ± 284.7	−121.7 ± 328.1	−9.2 ± 284.7	0.2437

FA, fluorescein angiography; GLD, greatest linear dimension of the entire lesion; logMAR, logarithm of the minimum angle of resolution; VA, visual acuity; VEGF, vascular endothelial growth factor.

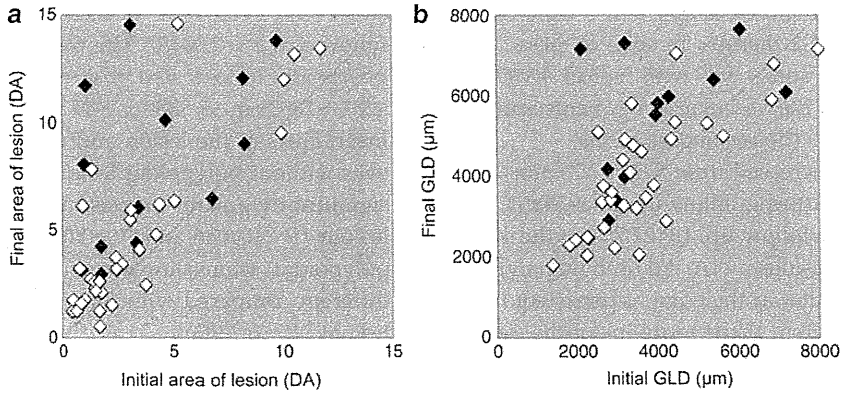

Figure 1 (a) Correlation between initial and final areas of the lesion in eyes with typical age-related macular degeneration. Initial areas are significantly correlated with final areas of the lesion ($R = 0.7347$, $P < 0.0001$). (b) Correlation between initial and final greatest linear dimension (GLD) in eyes with typical age-related macular degeneration. Initial GLD is significantly correlated with final GLD ($R = 0.7349$, $P < 0.0001$). One disc area (DA) is estimated to be 2.54 mm^2 on the basis of one optic disc diameter being 1.8 mm. Open diamonds represent eyes without polypoidal lesions, and closed diamonds represent eyes with polypoidal lesions.

8.68 ± 7.75 mm^2 and 3850 ± 1627 mm, respectively. Figure 1 shows the relationship of area of the lesion and of the GLD obtained at the initial visit and at final examination. The initial area of the lesion ($R = 0.7347$, $P < 0.0001$) and initial GLD ($R = 0.7349$, $P < 0.0001$) were correlated closely with final values.

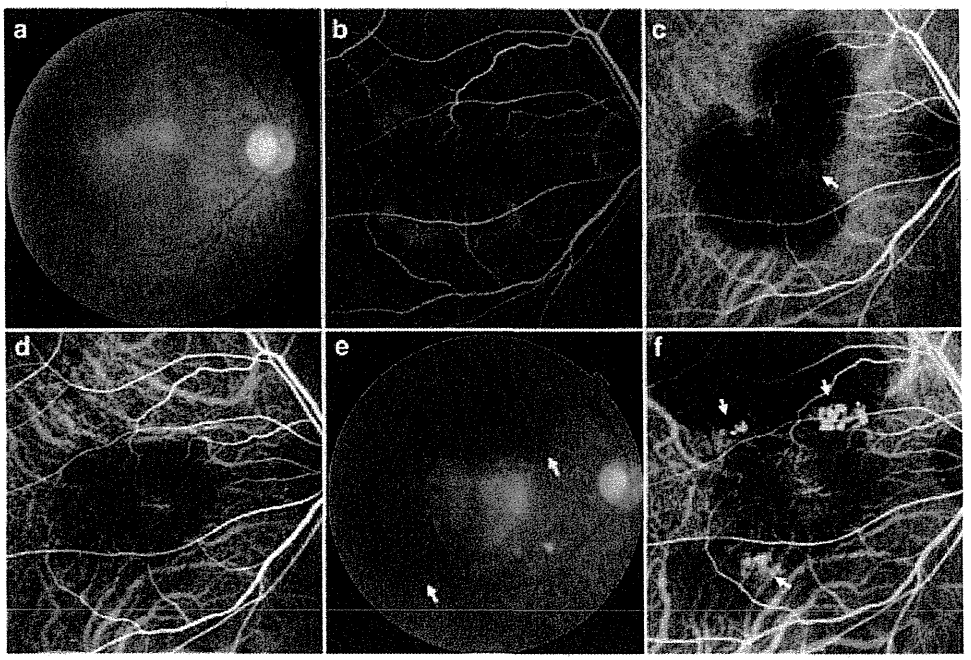

Figure 2 Development of polypoidal lesions at the border of persistent choroidal neovascularization (CNV) in a right eye with typical age-related macular degeneration. (a) Fundus photograph at the initial visit shows a multi-lobed serous pigment epithelial detachment (PED). Visual acuity was 0.8 in this eye. (b) Fluorescein angiography (FA) at the initial visit shows only hyperfluorescent areas associated with the PED. (c) Indocyanine green angiography (IA) shows CNV (arrow) at the edge of the PED; no polypoidal lesions are seen. (d) Fundus photograph at 34 months after the initial visit. With two photodynamic treatments, activity of the CNV has regressed. Visual acuity was now 0.2 in the right eye. (e) At 50 months after the initial visit, new serosanguineous PEDs (arrows) have developed at the upper side and at the inferotemporal side of the subfoveal disciform scar. (f) IA shows multiple polypoidal lesions (arrows) at the edge of the persistent CNV. Visual acuity was 0.1 in this eye.

At the initial visit, although all eyes of the patients involved showed classic and/or occult CNV associated with AMD, no eyes showed polypoidal lesions by IA. During the follow-up period, 34 eyes were initially treated with photodynamic therapy, and 5 were initially treated with anti-VEGF therapy. In spite of these treatments, however, some eyes with typical AMD showed extension of the vascular components with an exudative change. The mean area of the neovascularization increased from $8.68 \pm 7.75\,mm^2$ to $14.28 \pm 10.57\,mm^2$ during follow-up ($P<0.0001$). Moreover, during the follow-up, 13 (27.7%) of the 47 eyes showed polypoidal lesions by IA. All of these polypoidal lesions developed either at the edge of persistent CNV (Figure 2) or, more often, at the terminus of the newly progressed CNV (Figures 3 and 4). Of 12 eyes with a final CNV area >8 DA, 7 (58.3%) showed newly developed polypoidal lesions (Figure 1).

Depending on the development of polypoidal lesions, we divided our patients with typical AMD into two groupsF those with polypoidal lesions ($n=13$) and those without polypoidal lesions ($n=34$). Table 1 shows baseline and final measurement values of each group. There were no significant differences in gender or age between these two groups ($P=0.9739$ and $P=0.8913$). Furthermore, there were no differences in VA ($P=0.6234$), area of lesion ($P=0.3262$), or GLD ($P=0.3269$) at the initial visit. The mean area of the lesion in eyes with polypoidal lesions enlarged significantly from $10.50 \pm 7.88\,mm^2$ to $20.87 \pm 10.21\,mm^2$ during the follow-up ($P=0.0018$). The mean GLD in eyes with polypoidal lesions also progressed significantly from $4231 \pm 1692\,mm$ to $5880 \pm 1947\,mm$ ($P=0.0032$). Although mean areas of the lesion and GLD were increased in eyes without polypoidal lesions, the increases were significantly greater in eyes that developed polypoidal lesions ($P=0.0036$ and $P=0.0035$). In eyes with polypoidal lesions, however, final VA was not statistically different compared with that in eyes without polypoidal lesions ($P=0.2303$).

Discussion

PCV was first described as a new clinical entity with an associated unique form of choroidal vascular abnormality.[1–3] Subsequently, however, based on histological specimens and OCT examinations, PCV is considered to be a unique form of CNV.[25,26] In general, presumed exudative AMD is diagnosed as PCV when IA shows polypoidal lesions at the terminus of the

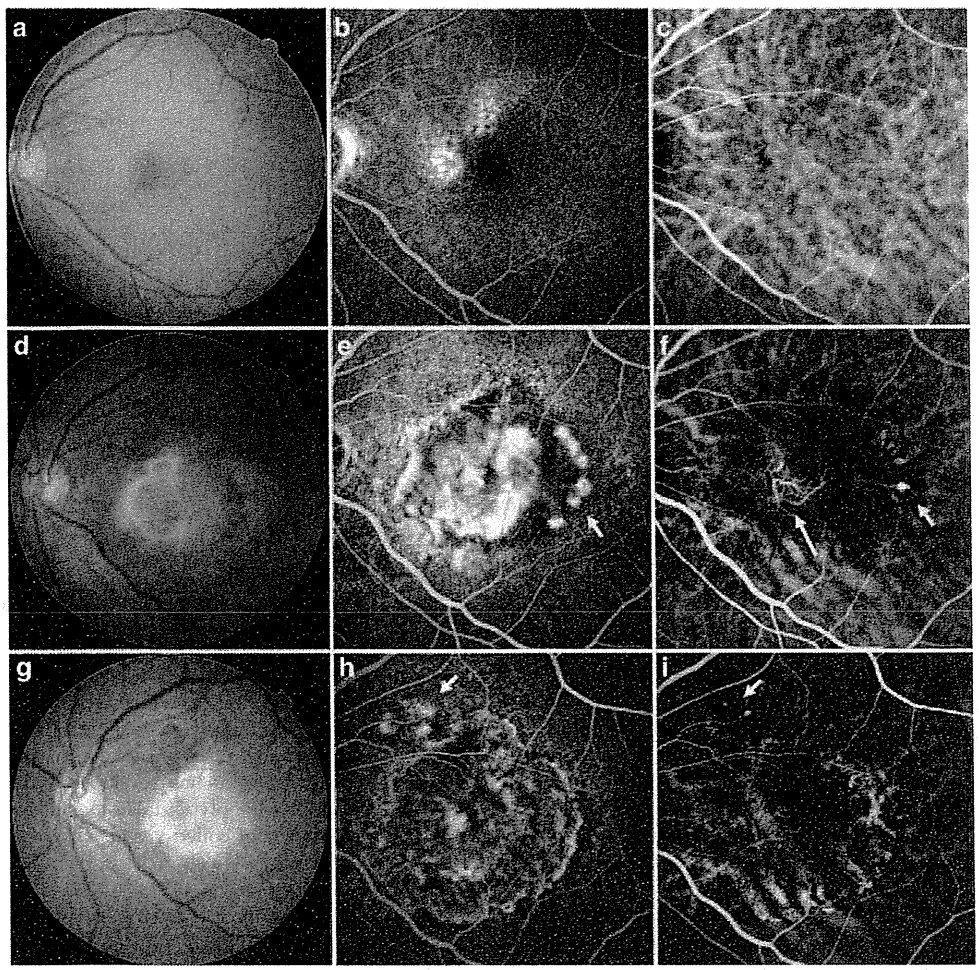

Figure 3 Development of polypoidal lesions at the terminus of newly progressed choroidal neovascularization (CNV) in a left eye with typical age-related macular degeneration. (a) Fundus photograph at the initial visit; at which time visual acuity in this eye was 1.2. (b) Fluorescein angiography (FA) at the initial visit shows inactive occult CNV. (c) Indocyanine green angiography (IA) shows no polypoidal lesions. (d) At 34 months after the initial visit, visual acuity had decreased to 0.15. Fundus photograph shows an active exudative change at the temporal side of a subfoveal disciform scar. (e) FA shows large subfoveal classic CNV with temporal active leakage from the CNV (arrow). (f) IA shows mature subfoveal CNV (long arrow). The CNV has progressed temporally and now forms multiple terminal bulbs, which are seen as polypoidal lesions (arrow). Three intravitreal injections of bevacizumab caused activity of the CNV to regress. (g) At 64 months after the initial visit, a new active lesion has developed on the upper border of the subfoveal disciform scar. Visual acuity, however, remained at 0.15. (h) FA shows newly-developed CNV (arrow). (i) IA shows what are presumed to be newly developed polypoidal lesions (arrow).

branching vascular network.[8] In PCV, IA is essential to make the diagnosis and to precisely evaluate the entire vascular lesion.[8] In the current study, polypoidal lesions developed in 27.7% of eyes with typical AMDF eyes that had shown no polypoidal lesions at the initial visit. All polypoidal lesions developed at the edge of persistent CNV or, more often, at the terminus of recently progressed CNV. The current observation suggests that active AMD may show polypoidal lesions, if there is progression in the subretinal pigment epithelium space.

The tip of the extending CNV, which is the most active lesion, typically shows vigorous leakage on FA.[22] Even if the CNV is located beneath the retinal pigment epithelium, it sometimes shows a 'classic' appearance, as proposed in the updated clinicopathological classification of subretinal neovascularization by Gass.[27] As molecules of indocyanine green readily attach to serum albumin,[28] vigorous leakage is not seen usually by IA, even from active CNV,[23,24,29] but CNV that is stained by indocyanine green may well appear as knobbed hyperfluorescent spots on IA.[30] In our patients, the tips of progressive CNV associated with AMD that showed focal hyperfluorescence on IA might appear to be polypoidal lesions.

Another interpretation is also possible. We can assume that the branching vascular network and polypoidal lesions represent a variant of type 1 CNV associated with exudative AMD.[4,5] In the clinical setting, when no

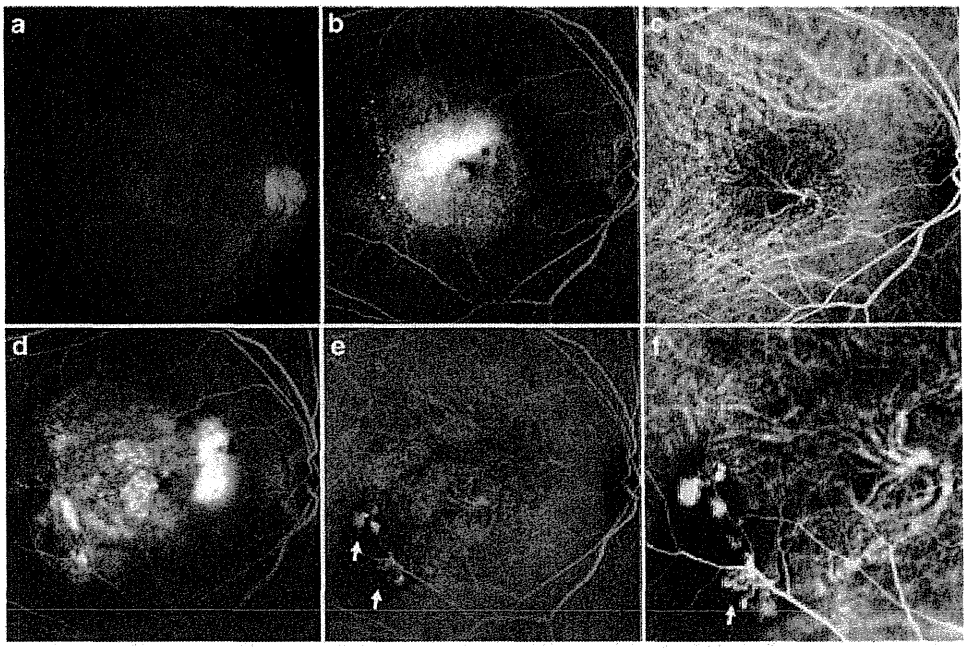

Figure 4 Development of polypoidal lesions at the terminus of recently progressive choroidal neovascularization (CNV) in a right eye with typical age-related macular degeneration. (a) Fundus photograph at the initial visit shows atrophy of the retinal pigment epithelium. Visual acuity was 0.4 in the right eye. (b) Fluorescein angiography (FA) at the initial visit shows subfoveal occult CNV. (c) Indocyanine green angiography (IA) shows CNV beneath the fovea, but no polypoidal lesions are seen. With photodynamic therapy, activity of the CNV regressed. (d) At 24 months after the initial visit, a new active lesion has developed at the temporal side of the regressed CNV. Visual acuity at this time was 0.4 in the right eye. (e) IA reveals multiple polypoidal lesions (arrows) at the edge of the progressive CNV. (f) Magnified IA shows that some of the polypoidal lesions consist of coiled vessels (arrow).

polypoidal lesions are seen, it is difficult to distinguish the branching vascular network from the type 1 CNV that may be associated with AMD.[31] Clinically, some polypoidal lesions do regress spontaneously or, more commonly, after photodynamic therapy, but they tend to recur at the same location or at other terminals of the branching vascular network.[6,9,32] In the current study, a diagnosis of typical AMD was made in all eyes, based on the initial IA. It is possible that some of our patients actually had PCV which was misdiagnosed, and that some showed polypoidal lesions during the follow-up. Recently, Maruko *et al*[33] reported that among 349 patients with neovascular AMD, 20 (5.7%) had 1 eye with PCV, whereas the fellow eye showed typical AMD, but that PCV developed during the follow-up in 10 eyes that had typical AMD at the initial examination. As their patients had PCV lesions in the fellow eye, it is reasonable to assume that these eyes originally had PCV but did not meet the diagnostic criteria of PCV.[33]

Our patients had been examined with both FA and IA for more than 2 years after the initial visit. In the current study, the rate of those eyes that were refractory to treatment or that showed a recurrence of CNV after the successful initial treatment might be relatively high. Recently, Cho *et al*[19] reported that polypoidal lesions were detected in 12 cases of exudative AMD with a poor response to anti-VEGF therapy. In their report, treatment with photodynamic therapy, photodynamic therapy/anti-VEGF combination therapy, or continued anti-VEGF monotherapy resulted in complete resolution of exudation in 9 of 12 eyes. In the current study, we showed that typical AMD refractory to treatment sometimes developed polypoidal lesions at the terminus of the newly progressed CNV. However, visual prognosis of these eyes was not poor. We treated eyes with polypoidal lesions primarily by photodynamic therapy or photodynamic therapy combined with anti-VEGF therapy. Today, anti-VEGF therapy is a primary treatment for typical AMD. In eyes with exudative AMD refractory to treatment, however, we suggest that clinicians should reconsider the treatment strategy after re-evaluation of the CNV by IA.

It is still controversial as to whether PCV is a distinct clinical entity or is simply a unique form of exudative AMD.[6] In Asian populations, a number of reports have shown that genetic variations in *ARMS2* and *CFH* are strongly associated with both AMD and PCV.[34–38] In addition, Lima *et al*[39] recently reported that the PCV phenotype in Caucasian patients is associated with the three major AMD-associated loci, including *CFH*, *ARMS2*, and *CFB/C2* genes, and they suggested that PCV and AMD are genetically similar in these tested loci.[39]

Although Kondo *et al*[40] have implicated the elastin gene as a susceptibility gene for PCV, it is generally believed that PCV and AMD share common genetic backgrounds, even though complications, treatment effect, and visual prognosis are somewhat different.[6,11] Indeed, PCV is a distinct clinical entity,[9] although some advanced AMD cases do show features characteristic of PCV.[33]

Limitations of the current study are its retrospective nature and the various treatment regimens used. In the current study, active AMD sometimes showed polypoidal lesions at the terminus of the vascular lesion, when the neovascularization showed progression in the subretinal pigment epithelium space. In the clinical setting, eyes with a small PCV lesion often maintain good VA for a protracted period of time.[41,42] In contrast, cases of PCV with a large lesion that has a poor response to treatment and that shows progression, tend to have a poor visual prognosis.[21] Our findings suggest that advanced AMD overlaps with PCVF at least with PCV that has a large vascular lesion.

Summary

- **What was known before**
  Polypoidal lesions at the terminus of the branching vascular network are a typical feature seen in polypoidal choroidal vasculopathy.

- **What this study adds**
  Polypoidal lesions sometimes occur in advanced exudative age-related choroidal neovascularization.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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