Graefes Arch Clin Exp Ophthalmol (2010) 248:361–368
DOI 10.1007/s00417-009-1276-2

RETINAL DISORDERS

Combined cases of polypoidal choroidal vasculopathy and typical age-related macular degeneration

Ichiro Maruko · Tomohiro Iida · Masaaki Saito · Dai Nagayama

Received: 23 August 2009 / Revised: 8 December 2009 / Accepted: 10 December 2009 / Published online: 14 January 2010

Abstract
Background When we classified neovascular exudative age-related macular degeneration (AMD) into three types of polypoidal choroidal vasculopathy (PCV), typical AMD, and retinal angiomatous proliferation (RAP) in our previous study, we reported 5.5% had the combined cases, such as one eye had PCV and the other eye had typical AMD. We examined the clinical characteristics of these combined cases in the current study.
Methods All cases underwent fluorescein and indocyanine green angiography (FA and ICGA) at the initial examination. All PCV cases were diagnosed definitively based on characteristic aneurysmal lesions seen on ICGA. Follow-up examinations also were conducted to determine whether polypoidal lesions had developed in the eyes with typical AMD.
Results Among 349 patients with neovascular AMD, 20 (5.7%) had one eye with PCV and the other eye with typical AMD. The average age was 73 years. The mean best-corrected visual acuity levels at the initial examination in eyes with PCV and typical AMD were 0.20 and 0.43, respectively (p=0.09). All subgroups of classic and occult CNV were observed in the eyes with typical AMD on FA. During the follow-up period (average, 21.7 months), PCV developed in ten eyes with typical AMD at the initial examination.
Conclusions Although some cases might include different stages of progression or probable cases of PCV, the combined cases in which one eye has PCV and the other eye has typical AMD suggest that those clinical entities are not independent and possibly overlap.

I. Maruko (✉) · T. Iida · M. Saito · D. Nagayama
Department of Ophthalmology,
Fukushima Medical University School of Medicine,
1 Hikarigaoka,
Fukushima 960-1247, Japan
e-mail: imaruko@fmu.ac.jp

Keywords Polypoidal choroidal vasculopathy · Age-related macular degeneration

Introduction

Neovascular exudative age-related macular degeneration (AMD) is a leading cause of legal blindness in elderly patients in developed countries. In Japan, fewer patients have neovascular AMD compared to Western countries [8, 9, 14, 17, 20]. However, the prevalence of AMD in Japan is increasing rapidly [15], and the demographic features differ from those in other countries.

We classified neovascular AMD in Japanese patients into three types and reported that among 289 patients, 158 (54.7%) were diagnosed with polypoidal choroidal vasculopathy (PCV), 102 (35.3%) with typical AMD, and 13 (4.5%) with retinal angiomatous proliferation (RAP) [13]. We concluded that neovascular AMD in Japanese patients has demographic features that differ from those in Caucasian patients. Each type is characterized by differences in clinical behavior, examination findings, and pathologic deductions. Accurate diagnoses of these types are important for appropriate patient management [2, 19]. However, we also reported that 16 patients (5.5%) had a combination of types, i.e., one eye had PCV and the other eye had typical AMD. These combined cases might indicate that these pathologies are not independent of each other. Because the proportion of PCV in neovascular AMD in Japan is more than 50%, cases with both PCV and typical AMD might be observed frequently.

In the current study, we examined the clinical characteristics of cases in which one eye had PCV and the other eye had typical AMD.

Patients and methods

The study followed the tenets of the Declaration of Helsinki. We retrospectively reviewed the medical records of the patients and there were no confidentiality issues. The institutional review board at Fukushima Medical University School of Medicine approved this retrospective analysis. All subjects provided written informed consent after the nature and possible consequences of the study were explained.

The patients with neovascular AMD in whom one eye had PCV and the other eye had typical AMD were evaluated retrospectively based on age, gender, and best-corrected visual acuity (BCVA) in each eye. The BCVA was measured with a Japanese standard decimal VA chart, and the mean BCVA was calculated using the logarithm of the minimum angle of resolution (logMAR) scale. The clinical examination included indirect ophthalmoscopy, slit-lamp biomicroscopy with a contact lens, or noncontact lens (e.g., 60 diopters), and color and red-free fundus photography. All participants were examined by digital fluorescein angiography (FA) and indocyanine green angiography (ICGA) at the initial examination. We used a digital imaging system with an infrared camera and standard fundus camera (TRC-50 IX/IMAGEnet H1024 system, Topcon, Tokyo, Japan) and a confocal laser scanning system (HRA-2, Heidelberg Engineering, Dossenheim, Germany). All angiograms were evaluated by three retina specialists (I.M., T.I., M.S.) masked to the clinical findings. We measured the lesion area in eyes with PCV and typical AMD on the FA images using IMAGENet 2000 software (Topcon). The lesion area was defined as the area of leakage caused by neovascularization and features obscuring the boundaries, including blocked fluorescence due to blood, thick exudate, hypertrophic retinal pigment epithelium (RPE), and associated pigment epithelial detachment (PED) on FA. The lesion area was measured in disc areas (DA), with one DA calculated as 2.54 mm^2 based on a standard disc diameter of 1.8 mm [1, 18]. All cases were observed by optical coherence tomography (OCT) to confirm RPE elevation and retinal morphologic changes. The following definitions were used to describe the related clinical and angiographic abnormalities evaluated in the current study.

The diagnostic criteria for PCV in the current study were proposed based on ICGA findings, which visualized the characteristic aneurysmal lesions. The Japanese Study Group of Polypoidal Choroidal Vasculopathy [7] defined the following criteria: protruded orange-red elevated lesions (excluding PED, choroidal hemangioma, and subretinal blood) observed by fundus examination and characteristic aneurysmal lesions seen on ICGA. However, only definitive cases of PCV on ICGA were included in the current study for unequivocal diagnosis. All patients with PCV were diagnosed as having neovascular AMD on FA, and then it was identified as PCV on ICGA.

The typical AMD lesion area was comprised of classic choroidal neovascularization (CNV) on FA and defined as follows: predominantly classic CNV, neovascular lesions in which the classic CNV component was greater than 50% of the total lesion area; minimally classic CNV, lesions in which the classic CNV components were less than 50% of the total lesion area; and occult CNV with no classic CNV component [2, 18]. Patients with other macular diseases such as high myopia, angioid streaks, and central serous chorioretinopathy were excluded.

All participants were examined and evaluated clinically by digital FA, ICGA, and OCT during the follow-up examinations. If polypoidal lesions developed in the eyes with typical AMD, we specified the location at which a polypoidal lesion developed during the follow-up period.

The results of a comparison of BCVA and the lesion area between the eyes with PCV and the fellow eye with typical AMD were analyzed using the Student's *t*-test. $p<0.05$ was considered significant.

Results

Among 349 patients with neovascular AMD examined between 2003 and 2005 at Fukushima Medical University Hospital, Fukushima, Japan, 20 patients (5.7%) in whom PCV was present in one eye and typical AMD in the fellow eye at the initial examination were included (16 men, four women; average age, 73 years). All patients were newly diagnosed with bilateral neovascular AMD. Although the combined cases should be defined as those in which each eye had a different type of neovascular AMD (i.e., PCV, typical AMD, or RAP), there were no cases with PCV and RAP or with typical AMD and RAP. Sixteen of the 20 patients had been included in our previous report [7]. Imaging procedures were performed successfully for all patients.

Table 1 shows the characteristics of the combined cases of PCV and typical AMD in the current study. The mean BCVA levels at the initial examination in eyes with PCV and typical AMD were 0.20 (0.71 logMAR) and 0.43 (0.37 logMAR) ($p=0.09$), respectively. The eyes with typical AMD were classified as one eye with predominantly classic CNV, five eyes with minimally classic CNV, and 14 eyes with occult with no classic CNV on FA. All subgroups classified according to classic CNV component on FA were observed in the eyes with typical AMD. The mean lesion area (DA) in eyes with PCV was larger than in eyes with typical AMD (10.8 ± 9.2 and 5.9 ± 3.9, respectively; $p=0.03$).

The 20 patients in the current study also underwent follow-up examinations after the initial examination (average follow-up period, 21.7 months; range, 2–48 months). In 20

Table 1 Clinical characteristics of combined cases in which one eye has PCV and the other eye has typical AMD

Patient no.	Sex	Age	Eyes with PCV			Eyes with Typical AMD					F/U (mo)
			Eye	BCVA at baseline	Lesion area (DA)	Eye	BCVA at baseline	Lesion area (DA)	Subgroup[a] on FA	develop PCV†	
1	M	76	OD	0.07	25.7	OS	0.3	5.8	ON	Yes	48
2	M	68	OD	0.8	10.6	OS	0.1	9.6	ON	Yes	6
3	M	62	OS	0.5	6.6	OD	0.5	3.0	ON	Yes	30
4	M	72	OD	0.5	11.2	OS	1.5	10.8	ON	Yes	6
5	M	75	OD	0.2	5.9	OS	0.7	2.5	ON	Yes	18
6	M	70	OD	0.02	7.9	OS	0.15	15.9	MC	Yes	30
7	M	82	OS	0.09	5.2	OD	0.04	6.1	MC	Yes	18
8	F	67	OS	0.06	11.8	OD	0.1	6.4	MC	Yes	2
9	M	79	OS	1.2	1.0	OD	0.3	8.1	MC	Yes	36
10	M	83	OD	0.1	3.7	OS	1.5	1.3	MC	Yes	30
Mean (1–10)		74		0.19	9.0±6.8		0.24	7.0±4.4			21.6
11	M	67	OS	0.03	29.4	OD	0.2	7.9	ON	No	18
12	M	75	OD	0.1	9.0	OS	0.4	4.4	ON	No	36
13	M	75	OS	1.2	2.2	OD	0.2	2.6	ON	No	30
14	M	75	OS	0.5	2.8	OD	0.9	1.5	ON	No	30
15	F	81	OS	0.1	27.2	OD	0.7	3.4	ON	No	24
16	F	53	OS	1.5	6.0	OD	1.2	3.2	ON	No	18
17	M	82	OS	0.05	19.7	OD	1.2	11.5	ON	No	6
18	M	82	OS	0.04	23.6	OD	0.7	3.4	ON	No	18
19	M	71	OD	0.3	3.9	OS	1.0	2.5	ON	No	6
20	F	66	OS	1.2	2.0	OD	1.0	7.2	PC	No	24
Mean (11–20)		73		0.18	12.6±11.1		0.60	4.8±3.1			20.7
Mean all		73		0.20	10.8±9.2		0.43	5.9±3.9			21.7

PCV = polypoidal choroidal vasculopathy; OS = left eye; OS = right eye;

AMD = age-related macular degeneration;

BCVA = best-corrected visual acuity. Mean BCVA was calculated using the logarithm of the minimum angle of resolution (logMAR) scale

Lesion area (DA) = the lesion size (DA) of eyes with PCV and typical AMD was measured from fluorescein and Indocyanine green angiography

DA = disc area

One DA = 2.54 mm^2 based on a standard disc diameter (DD) of 1.8 mm

FA = fluorescein angiography

MC = Minimally classic CNV

ON = Occult with no classic CNV

PC = Predominantly classic CNV

CNV = choroidal neovascularization

F/U (mo) = duration of follow-up period (months)

[a] The area of the lesion of typical AMD was composed of classic choroidal neovascularization (CNV) on fluorescein angiography and evaluated as follows:

predominantly classic CNV: a neovascular lesion in which the classic CNV component was greater than 50% of the total lesion size;

minimally classic CNV: lesions in which the classic CNV components were less than 50% of the total lesion size;

occult with no classic CNV: lesions in which there was no classic CNV component.

†develop PCV = development of PCV; The PCV cases appear the polypoidal lesion in the eyes with typical AMD during the follow-up period.

eyes with typical AMD diagnosed at the initial examination, PCV developed angiographically and clinically in ten eyes during the follow-up period (Table 1). Eight of 20 eyes with typical AMD diagnosed at the initial examination underwent photodynamic therapy (PDT) or laser photocoagulation during the follow-up period. Among the eyes with typical AMD, PCV was observed in four of eight treated eyes and six of 12 untreated eyes in the eyes at the initial examination.

There was no significant difference due to therapy in development of PCV among the eyes with typical AMD at the initial examination. A polypoidal lesion on ICGA developed from the edge of the original CNV at the initial examination in seven eyes and emerged from the area within the original CNV at the initial examination in three eyes.

Case reports

Case 1 was that of a 67-year-old man (patient 11) who reported visual loss in the left eye a few years previously and acute visual loss in the right eye. The BCVA at the initial examination was 0.2 (0.70 logMAR) in the right eye

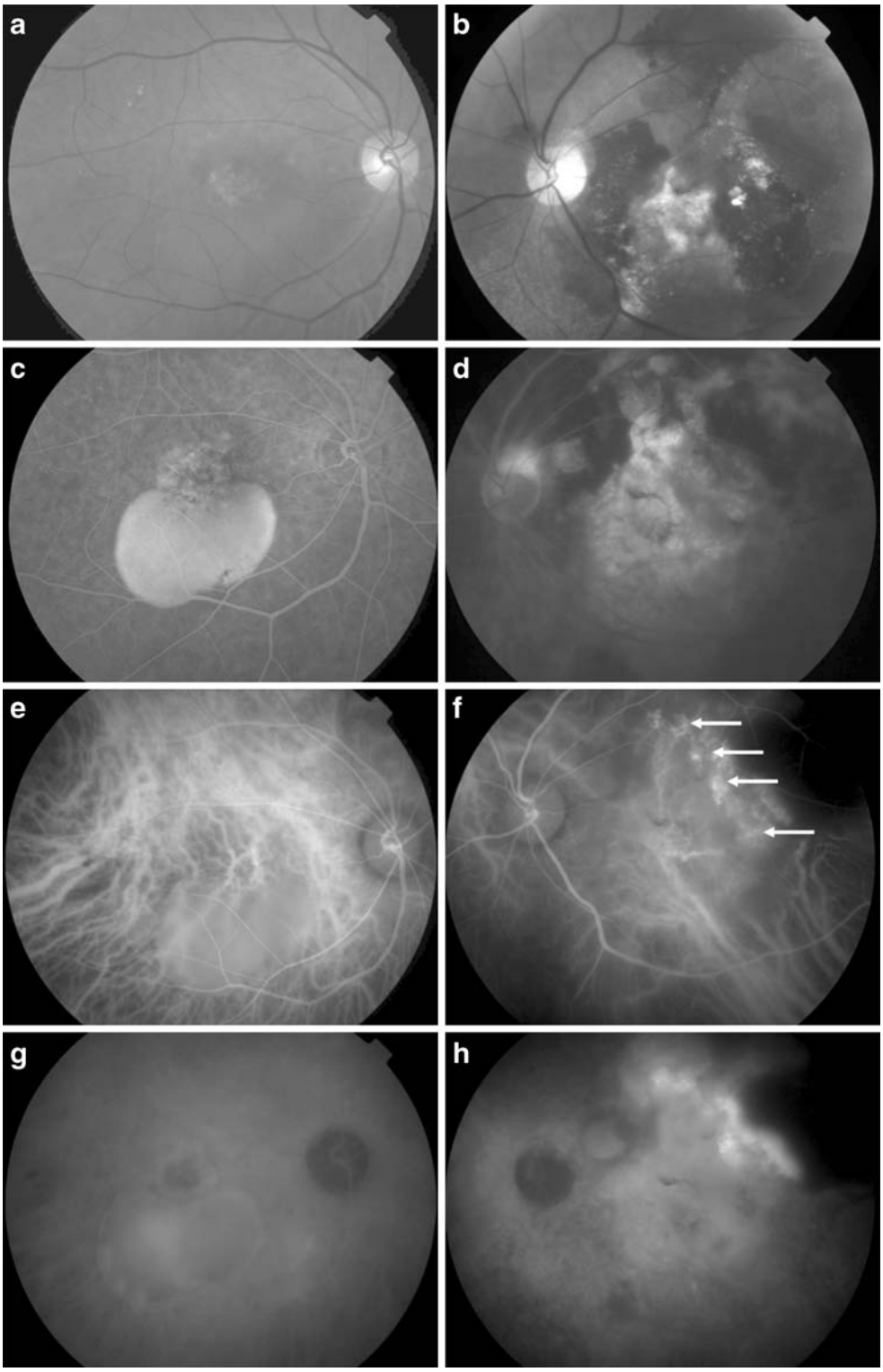

Fig. 1 Case 1 (patient 11). A 67-year-old man is representative of the combined cases of PCV and AMD in which the right eye has occult with no classic CNV and left eye has PCV. **a**, **b** A red-free fundus photograph showing RPE degeneration with a large PED in the right eye and an extensive exudative lesion with hard exudates and subretinal hemorrhage in the left eye. **c**, **d** FA shows occult CNV that includes the fovea with a large PED at the inferior fovea in the right eye and occult CNV with large fibrovascular PED in the left eye. Early phase (**e**, **f**) and late-phase (**g**, **h**) ICGA images showing hyperfluorescence corresponding to the PED in the right eye and a polypoidal lesion (*arrows*) at the superior temporal fovea in the left eye. There is no evidence of PCV in the right eye during early and late-phase ICGA

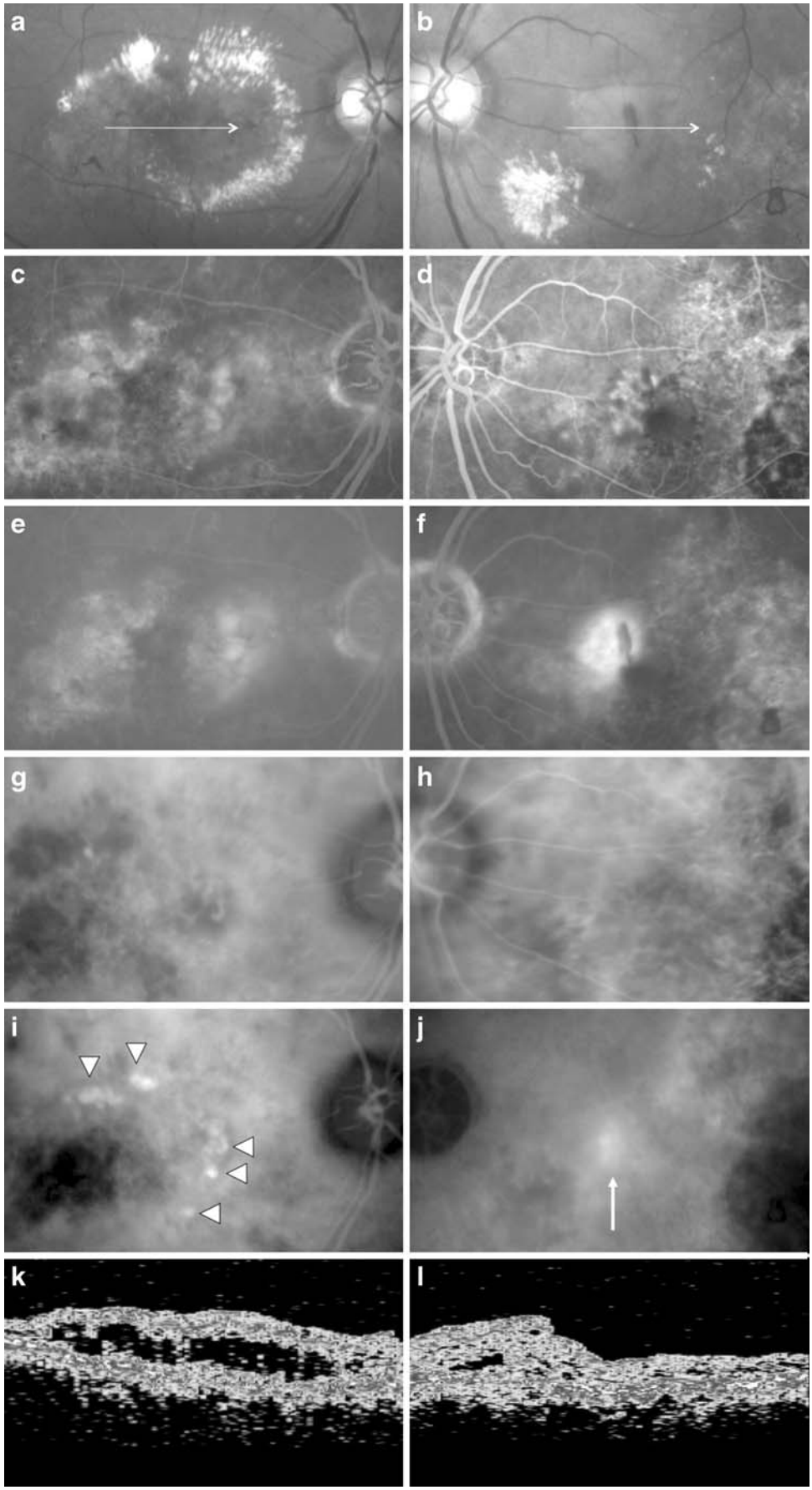

Fig. 2 Case 2 (patient 6). A 70-year-old man is representative of a combined case in which the right eye has PCV and the left eye has minimally classic CNV at the initial examination. **a**, **b** A red-free fundus photograph showing a gray-green lesion in the macular area surrounded by circinate exudates in the right eye and an extensive exudative lesion with a subretinal hemorrhage in the left eye. Early phase (**c**, **d**) and late-phase (**e**, **f**) FA images show minimally classic CNV nasal to the fovea bilaterally. Early phase (**g**, **h**) and late-phase (**i**, **j**) ICGA images show polypoidal lesions (*arrowhead*) at the outside edge of the area corresponding to the occult CNV on FA in the right eye and hyperfluorescence (*arrow*) nasal to the fovea in the left eye, which is the same area of classic CNV component on FA. There is no evidence of PCV in the left eye at the initial examination. OCT shows a serous retinal detachment in the right eye (**k**) and the hyperreflective tissue without RPE elevation at the gray-green lesion in the left eye (**l**). OCT images correspond to *horizontal white line* of (a) and (b)

and 0.03 (1.52 logMAR) in the left eye. There was RPE degeneration with a large PED in the right eye and an extensive exudative lesion with hard exudates and subretinal hemorrhages in the left eye. FA showed occult CNV that included the fovea with a large PED at the inferior fovea in the right eye and occult CNV with a large fibrovascular PED in the left eye. ICGA showed a polypoidal lesion at the superior temporal area of the fovea in the left eye. The lesion areas (DA) in eyes with typical AMD (right eye) and PCV (left eye) were 7.9 and 29.4, respectively. Although it was possible that PCV could develop in the future, there was no evidence of PCV in the right eye during the follow-up period (18 months). In this combined case of PCV and AMD, the right eye had occult CNV and the left eye had PCV (Fig. 1).

Case 2 was that of a 70-year-old man (patient 6) who had visual loss in the right eye a few years previously and sudden visual loss in the left eye. The BCVA at the initial examination was 0.15 (0.82 logMAR) in the right eye and 0.02 (1.70 logMAR) in the left eye. There was an elevated orange-red lesion in the macular area surrounded by circinate exudates in the right eye and an extensive exudative lesion that was partially gray-green with a subretinal hemorrhage in the left eye. FA showed minimally classic CNV; classic CNV was nasal to the fovea surrounded by occult CNV bilaterally. ICGA showed polypoidal lesions at the marginal edge of the area corresponding to the occult CNV on FA in the right eye. OCT showed a serous retinal detachment in the right eye and hyperreflective tissue without elevated RPE, indicating type 2 CNV above the RPE at the gray-green lesion in the left eye. There was no evidence of PCV in the left eye at the initial examination. The lesion areas (DA) in the right eye with PCV and the left eye with typical AMD were 15.9 and 7.9, respectively. In this combined case of PCV and AMD, the right eye had PCV and left eye had the minimally classic CNV of typical AMD at the initial examination. Although there was no leakage from the classic CNV in the left eye on FA after two applications of PDT, a polypoidal lesion was seen after 2.5 years on ICGA temporal to the fovea and separate from the original classic CNV. OCT temporal to the fovea in the left eye showed an elevated dome-shaped RPE corresponding to a polypoidal lesion on ICGA. PCV developed bilaterally during the 30-month follow-up period (Figs. 2 and 3).

Discussion

The current study showed that combined cases of PCV and typical AMD can develop in patients with neovascular AMD in which one eye has PCV and the other eye has typical AMD. We identified these combined cases in 5.7% of the patients with neovascular AMD. Fifty percent of cases with typical AMD at the initial examination had a polypoidal lesion on ICGA during the follow-up period despite PDT or

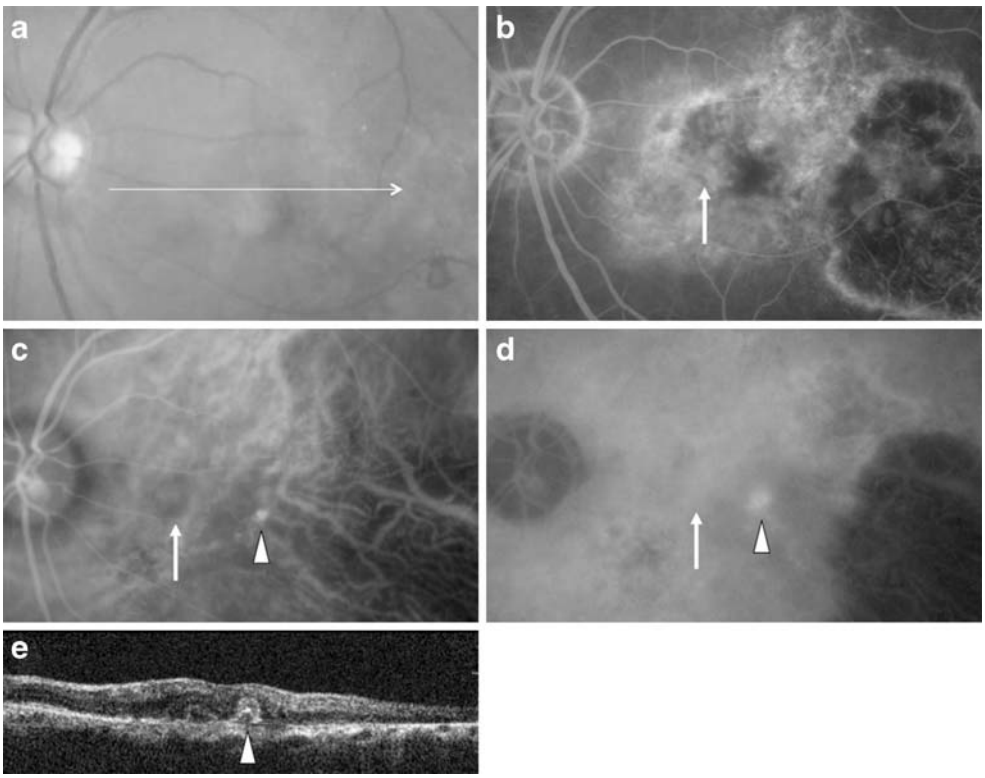

Fig. 3 Case 2. PCV in the left eye 2.5 years later in the same patient as in Fig. 2. **a** A red-free fundus photograph showing a gray-green lesion in the macular area without exudative lesion and subretinal hemorrhage. **b** FA shows no classic CNV. Early phase (**c**) and late-phase (**d**) ICGA images showing a polypoidal lesion (*arrowheads*) temporal to the fovea. *Arrows* in (b), (c), and (d) indicate the area corresponding to the classic CNV component on FA in the left eye in Fig. 2. **e** An OCT image temporal to the fovea in the left eye shows a dome-shaped RPE elevation (arrowhead) corresponding to a polypoidal lesion on ICGA. The OCT image corresponds to the horizontal white line in (a)

laser photocoagulation. However, these developments might be visible only angiographically, and clinical changes during the follow-up period, i.e., the pathological and intrinsic changes, were not evident.

Although the study was not population-based, we reported that the proportion of PCV is more than 50% in Japanese patients with neovascular AMD, and that PCV and typical AMD are male predominant, unilateral, and without large drusen in the fellow eye [13]. Thus, both PCV and typical AMD have similar demographic features and might be the same disease group with different clinical expressions. It is interesting that in some combined cases, one eye had PCV and the other eye had typical AMD under the same systemic conditions in the current study.

The Hisayama study reported that the prevalence of drusen was 9.8% in Japanese people [17]. This is a very small percentage compared to reports from Western countries. Although Japanese patients do not have much drusen, basal laminar deposits, which are recognized as a lesion of age-related maculopathy, were observed in elderly Japanese patients and Caucasian patients [6]. In addition, one of the major and important neovascular AMD genes, the *HtrA serine peptidase 1* (*HTRA1*) gene at location 10q26, has been identified in both Caucasian and Chinese patients [3, 21]. *HTRA1* also has been reported equally in Japanese patients with AMD [16, 22]. Some researchers have reported that the LOC387715/HTRA1 variants or ARMS2 (age-related maculopathy susceptibility 2)/HTRA1 variants were associated with PCV and typical AMD in a Japanese population, which suggested that PCV and typical AMD are similar in genetic susceptibility [4, 5, 11]. Although a large number of patient studies are needed, the elastin gene haplotype was reported to be associated with the different phenotypes of PCV and typical AMD [10]. Ladas and associates [12] reported that polypoidal lesions developed in patients with Doyne's familial honeycomb choroiditis, which is usually thought to occur with inherited, drusen-related, secondary CNV instead of PCV. This might indicate that the development to either PCV or typical AMD is not based on genetic factors only.

The eyes with PCV had a lower mean BCVA and a larger mean lesion area than the eyes with typical AMD at the initial examination. Most PCV cases had a better prognosis; however, some cases with recurrent bleeding and exudation had a poor prognosis. In the combined cases in the current study, the eyes with PCV seemed to have an unfavorable prognosis. Meanwhile, the eyes with typical AMD might have had a favorable prognosis. However, the eyes that developed to polypoidal lesions had a lower BCVA and a larger lesion area than the eyes that did not develop polypoidal lesion in the eyes with typical AMD. These differences in the mean BCVA and lesion area might depend on the duration of the disorder in the combined cases.

The diagnostic criteria for PCV have not yet been established in the presumed PCV cases without polypoidal lesions. In the Japanese Study Group of Polypoidal Choroidal Vasculopathy [7], probable cases of PCV were defined by the presence of at least one of the following: only an abnormal vascular network seen on ICGA and recurrent hemorrhagic and/or RPE serous detachments. In the current study, half of the eyes with typical AMD diagnosed at the initial examination had a polypoidal lesion on ICGA during the follow-up period (range, 2–48 months). Some eyes with typical AMD might be diagnosed as probable cases based on the Japanese Study Group of Polypoidal Choroidal Vasculopathy [7]. Only patients with an abnormal vascular network of PCV without a polypoidal lesion on ICGA might be considered as having occult CNV associated with typical AMD, because the abnormal vascular network of PCV often shows leakage on FA or ICGA. Thus, it is difficult even for retina specialists to distinguish the abnormal vascular network without a polypoidal lesion from CNV under the RPE (e.g., type 1 CNV). Further study is needed to accurately diagnose the probable cases of PCV in a clinical setting.

In conclusion, we observed combined cases in which one eye had PCV and the other eye had typical AMD in patients with neovascular AMD. Although some cases might include those with different stages or probable cases of PCV, the combined cases in the current study might imply that both clinical entities are not independent and possibly overlap.

Funding None.

Competing interests None.

References

1. Ali F, Chan WC, Stevenson MR, Muldrew KA, Chakravarthy U (2004) Morphometric analysis of angiograms of exudative lesions in age-related macular degeneration. Arch Ophthalmol 122:710–715. doi:10.1001/archopht.122.5.710
2. Barbazetto I, Burdan A, Bressler NM, Bressler SB, Haynes L, Kapetanios AD, Lukas J, Olsen K, Potter M, Reaves A, Rosenfeld P, Schachat AP, Strong HA, Wenkstern A, Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study Group (2003) Verteporfin in Photodynamic Therapy Study Group. Photodynamic therapy of subfoveal choroidal neovascularization with verteporfin: fluorescein angiographic guidelines for evaluation and treatment–TAP and VIP report No. 2. Arch Ophthalmol 121:1253–1268. doi:10.1001/archopht.121.9.1253
3. Dewan A, Liu M, Hartman S, Zhang SS, Liu DT, Zhao C, Tam PO, Chan WM, Lam DS, Snyder M, Barnstable C, Pang CP, Hoh J (2006) HTRA1 promoter polymorphism in wet age-related macular degeneration. Science 314:989–992. doi:10.1126/science.1133807

4. Gotoh N, Nakanishi H, Hayashi H, Yamada R, Otani A, Tsujikawa A, Yamashiro K, Tamura H, Saito M, Saito K, Iida T, Matsuda F, Yoshimura N (2009) ARMS2 (LOC387715) Variants in Japanese Patients with Exudative Age-related Macular Degeneration and Polypoidal Choroidal Vasculopathy. Am J Ophthalmol 147:1037–1041. doi:10.1016/j.ajo.2008.12.036
5. Gotoh N, Yamada R, Nakanishi H, Saito M, Iida T, Matsuda F, Yoshimura N (2008) Correlation between CFH Y402H and HTRA1 rs11200638 genotype to typical exudative age-related macular degeneration and polypoidal choroidal vasculopathy phenotype in the Japanese population. Clin Exper Ophthalmol 36:437–442. doi:10.1111/j.1442-9071.2008.01791.x
6. Ishibashi T, Patterson R, Ohnishi Y, Inomata H, Ryan SJ (1986) Formation of drusen in the human eye. Am J Ophthalmol 101:342–353
7. Japanese Study Group of Polypoidal Choroidal Vasculopathy (2005) Criteria for diagnosis of polypoidal choroidal vasculopathy (in Japanese). Nippon Gannka Gakkai Zasshi 109:417–427
8. Klein R, Klein BE, Jensen SC, Meuer SM (1997) The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. Ophthalmology 104:7–21
9. Klein R, Klein BE, Tomany SC, Meuer SM, Huang GH (2002) Ten-year incidence and progression of age-related maculopathy: The Beaver Dam Eye Study. Ophthalmology 109:1767–1779. doi:10.1016/S0161-6420(02)01146-6
10. Kondo N, Honda S, Ishibashi K, Tsukahara Y, Negi A (2007) LOC387715/HTRA1 variants in polypoidal choroidal vasculopathy and age-related macular degeneration in a Japanese population. Am J Ophthalmol 144:608–612. doi:10.1016/j.ajo.2007.06.003
11. Kondo N, Honda S, Ishibashi K, Tsukahara Y, Negi A (2008) Elastin gene polymorphisms in neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. Invest Ophthalmol Vis Sci 49:1101–1105. doi:10.1167/iovs.07-1145
12. Ladas ID, Karagiannis DA, Georgalas I, Rouvas AA, Moschos MM, Apostolopoulos M (2004) Polypoidal choroidal vasculopathy associated with Doyne's familial choroiditis: treatment with thermal laser. Eur J Ophthalmol 14:264–268
13. Maruko I, Iida T, Saito M, Nagayama D, Saito K (2007) Clinical characteristics of exudative age-related macular degeneration in Japanese patients. Am J Ophthalmol 144:15–22. doi:10.1016/j.ajo.2007.03.047
14. Mitchell P, Wang JJ, Foran S, Smith W (2002) Five-year incidence of age-related maculopathy lesions: the Blue Mountains Eye Study. Ophthalmology 109:1092–1097. Erratum in: Ophthalmology (2002) 109:1588. doi:10.1016/S0161-6420(02)01055-2
15. Miyazaki M, Kiyohara Y, Yoshida A, Iida M, Nose Y, Ishibashi T (2005) The 5-year incidence and risk factors for age-related maculopathy in a general Japanese population: the Hisayama study. Invest Ophthalmol Vis Sci 46:1907–1910. doi:10.1167/iovs.04-0923
16. Mori K, Horie-Inoue K, Kohda M, Kawasaki I, Gehlbach PL, Awata T, Yoneya S, Okazaki Y, Inoue S (2007) Association of the HTRA1 gene variant with age-related macular degeneration in the Japanese population. J Hum Genet 52:636–641. doi:10.1007/s10038-007-0162-1
17. Oshima Y, Ishibashi T, Murata T, Tahara Y, Kiyohara Y, Kubota T (2001) Prevalence of age related maculopathy in a representative Japanese population: the Hisayama study. Br J Ophthalmol 85:1153–1157. doi:10.1136/bjo.85.10.1153
18. Treatment of Age-related Macular Degeneration With Photodynamic Therapy (TAP) Study Group (1999) Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials–TAP report. Arch Ophthalmol 117:1329–1345
19. Uyama M, Wada M, Nagai Y, Matsubara T, Matsunaga H, Fukushima I, Takahashi K, Matsumura M (2002) Polypoidal choroidal vasculopathy: natural history. Am J Ophthalmol 133:639–648. doi:10.1016/S0002-9394(02)01404-6
20. Vingerling JR, Dielemans I, Hofman A, Grobbee DE, Hijmering M, Kramer CF, de Jong PT (1995) The prevalence of age-related maculopathy in the Rotterdam Study. Ophthalmology 102:205–210
21. Yang Z, Camp NJ, Sun H, Tong Z, Gibbs D, Cameron DJ, Chen H, Zhao Y, Pearson E, Li X, Chien J, Dewan A, Harmon J, Bernstein PS, Shridhar V, Zabriskie NA, Hoh J, Howes K, Zhang K (2006) A variant of the HTRA1 gene increases susceptibility to age-related macular degeneration. Science 314:992–993. doi:10.1126/science.1133811
22. Yoshida T, DeWan A, Zhang H, Sakamoto R, Okamoto H, Minami M, Obazawa M, Mizota A, Tanaka M, Saito Y, Takagi I, Hoh J, Iwata T (2007) HTRA1 promoter polymorphism predisposes Japanese to age-related macular degeneration. Mol Vis 13:545–548