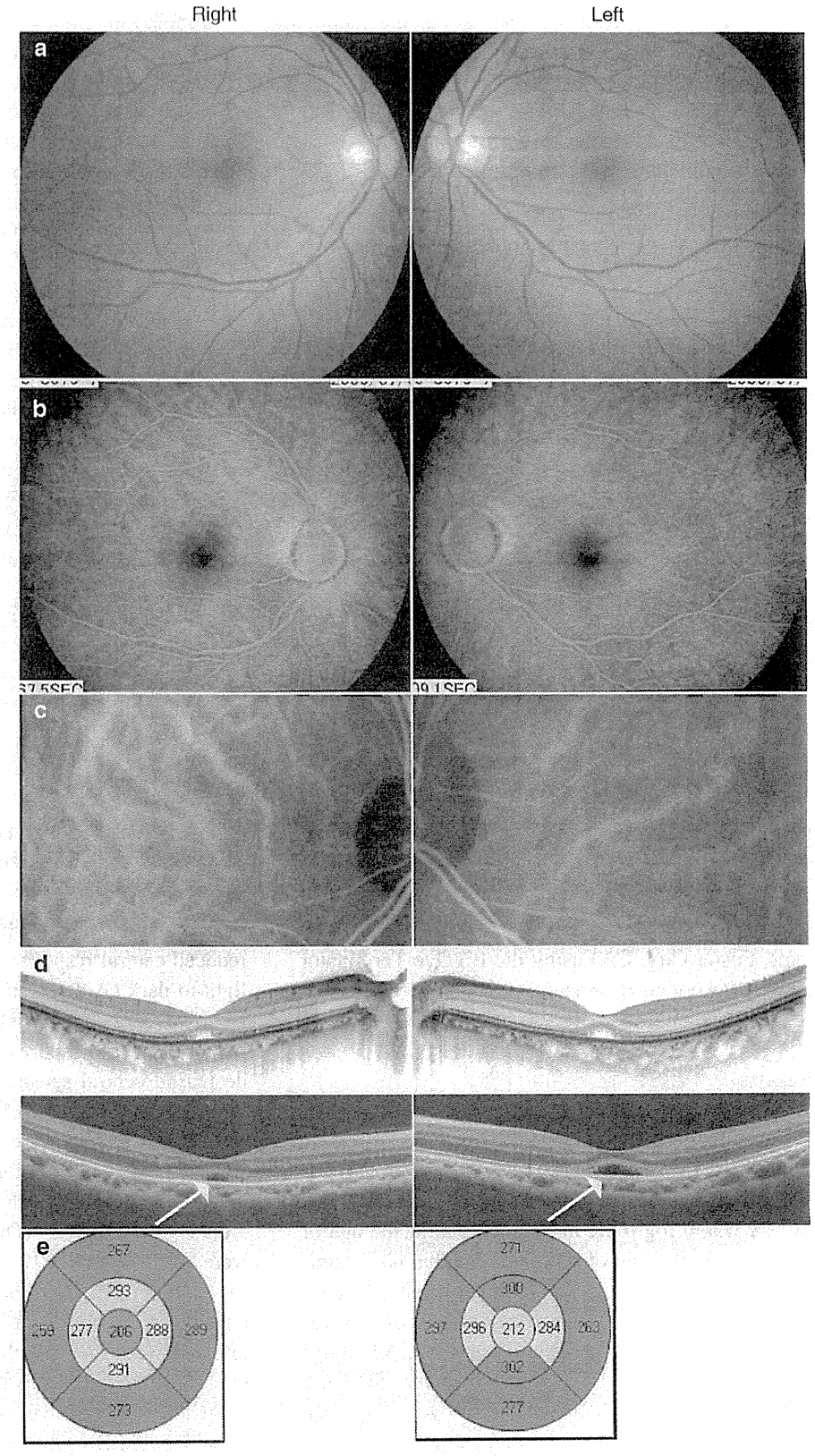

Fig. 1 Fundus photographs, fluorescein angiograms, and optical coherence tomography (OCT) findings. **a** Fundus photographs showing unremarkable findings in both eyes. **b** Late-phase fluorescein angiograms showing unremarkable findings in both eyes. **c** Middle-phase indocyanine green angiograms showing unremarkable findings in both eyes. **d** OCT images using SPECTRALIS (*top*) and HD 5-line scan (*bottom*) showing subretinal detachment (*arrows*) in the foveal areas only. **e** Macular thickness map of the Macular Cube protocol showing a slightly thin central retinal thickness of 206 μm (*right*) and 212 μm (*left*)

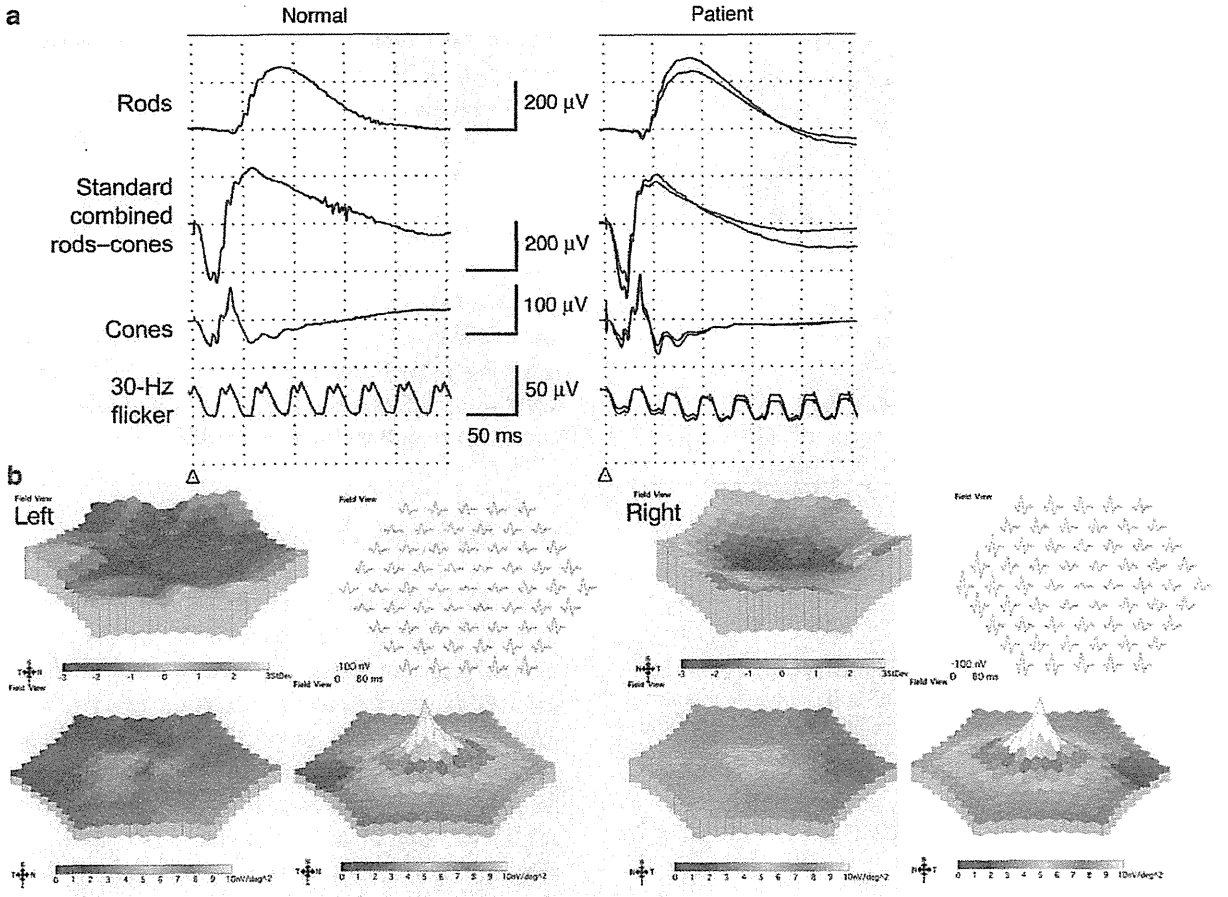

Fig. 2 Full-field ERG and multifocal ERG findings. **a** Full-field ERG showing normal 30-Hz flicker responses of rods, standard combined rods–cones, and cones. **b** Multifocal ERG revealed a reduced central response in both eyes

sequencer (3730xl DNA Analyzer; Applied Biosystems, Foster City, CA) using the BigDye Terminator kit V3.1 (Applied Biosystems).

Results

Case report

The patient underwent bilateral cataract surgery. His BCVA was 0 logMAR in both eyes until the age of 53 years. At the age of 55 years, ophthalmic examination was conducted at The Jikei University Hospital for progressive loss of visual acuity, and his BCVA was 0.15 in each eye. Funduscopy, FA, and ICGA findings were unremarkable (Fig. 1a–c). However, SD-OCT revealed subfoveal SRD in both eyes (Fig. 1d). Full-field ERGs showed normal responses for all components (Fig. 2a), while multifocal ERG revealed reduced central responses in both eyes (Fig. 2b). The light-to-dark (Arden) ratios of EOG were 2.46 in the right eye and 2.42 in the left eye, both within the normal range. The Humphrey Field Analyzer showed decreased central sensitivity; at the age of 56 years, the MD values were +0.51 (OS) and +0.67 (OD) dB, and the PSD values were 1.28 (OS) and 1.36 (OD) dB (Fig. 3a), indicating deteriorated central visual field defects. At the age of 58 years, the MD values were −0.90 (OS) and 0.29 (OD) dB, and the PSD values were 2.17 ($p < 0.02$) (OS) and 2.30 (OD) dB ($p < 0.02$) (Fig. 3b). The subfoveal SRD remained unchanged in both eyes (Fig. 1e). Based on these findings, we suspected inherited macular degeneration or chronic central serous chorioretinopathy (CSC).

At the age of 58 years, the patient visited Tokyo Kosei Nenkin Hospital seeking further treatment. His

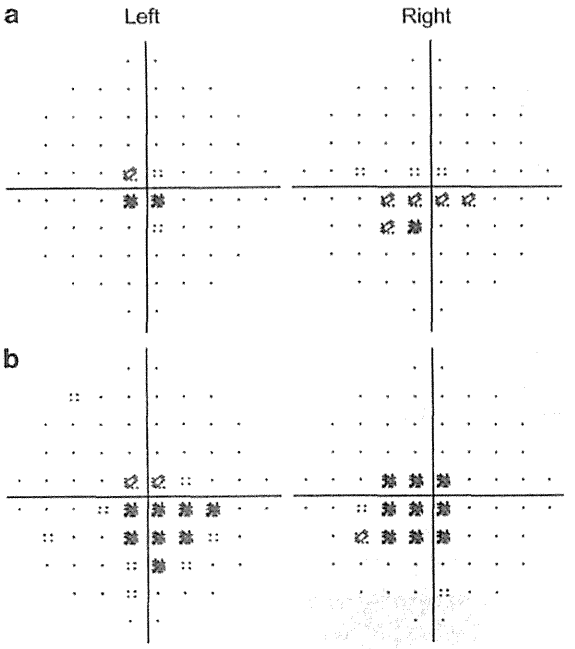

Fig. 3 Visual field in both eyes as measured by the Humphrey Field Analyzer with the central 10-2 SITA-Standard program. **a** Central visual field defects are visible. At 56 years old, the MD values were +0.51 (OS) and +0.67 (OD) dB, and the PSD values were 1.28 (OS) and 1.36 (OD) dB. **b** At 58 years old, the MD values were −0.90 (OS) and −0.29 (OD) dB, and the PSD values were 2.17 ($p < 0.02$) (OS) and 2.30 dB (OD) dB ($p < 0.02$)

logMAR BCVA was 0.532 in the right eye and 0.347 in the left eye, and SD-OCT showed subfoveal SRD in both eyes (Fig. 4). Although FA and ICGA yielded unremarkable findings, we could not exclude the possibility of chronic CSC. The patient, diagnosed as having chronic CSC, received 23 administrations of intravitreal bevacizumab (IVB; 1.25 mg) alternately in both eyes over a 2-year period (Fig. 4), and his subjective symptoms improved after each administration of IVB. He also underwent one treatment of reduced-fluence photodynamic therapy (RF-PDT) in each eye while receiving IVB but experienced no subjective improvements (Fig. 4). Two years after the first administration of IVB, when a partial posterior vitreous detachment (PVD) occurred, the vitreomacular adhesion (VMA) had disappeared. Therefore, IVB was discontinued owing to the reduction in SRD, and complete PVD was noted a few months later. As a result, logMAR BCVA showed slight improvement compared with the pre-IVB treatment levels. Three years after the first administration of IVB, logMAR BCVA was 0.155 in the right eye and 0.523 in the left eye. Central macular thickness (CMT) increased while undergoing IVB treatment (Fig. 4b). Four years after the first administration of IVB, he sought treatment to eliminate myodesopsia and underwent pars plana vitrectomy (Fig. 4).

Analysis of variance revealed that CMT after IVB (within 10 weeks) increased by 0.86 μm per week after IVB compared with pre-IVB treatment CMT ($p = 0.0040$), but logMAR BCVA and retinal detachment thickness were not significantly changed after receiving IVB. Furthermore, logMAR BCVA correlated with CMT ($r = -0.3881$, $p = 0.0012$) but not with SRD ($r = 0.0938$, $p = 0.4502$).

Molecular genetic findings

Since *RP1L1* mutations have been identified as the cause of autosomal dominant OMD, we investigated the possibility of *RP1L1*-associated autosomal dominant OMD in our patient. Mutation analysis of the *RP1L1* gene revealed the presence of a novel heterozygous variant (c.3595T>C in exon 4). This variant results in the substitution of proline (CCT) with serine (TCT) at amino acid position 1199 (p.S1199P) (Fig. 5), which has never been reported before [9–14]. Next, we used PolyPhen-2 and SANS Investigative Forensic Toolkit (SIFT; SANS™ Institute, Bethesda, MD) tools to predict the impact of the variant on protein function, and the results revealed "probable damage" with a score of 0.999 in PolyPhen-2 and "damage" with a score of 0 in SIFT. Based on these findings, we concluded that the variant is a disease-causing missense mutation. No other pathological variations of this gene were detected in our patient. The patient's brother and cousin also had decreased visual acuity but unfortunately blood samples were not available from family members. The missense mutation (p.S1199P) was not found in the dbSNP database (http://www.ncbi.nlm.nih.gov/SNP/), the 1,000 Genome Project database (http://www.1000genomes.org), the Exome Variant Server database (http://evs.gs.washington.edu/EVS/), or the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk). Therefore, the patient was finally diagnosed as having an atypical form of *RP1L1*-associated OMD, with the heterozygous mutation suggesting autosomal dominant inheritance.

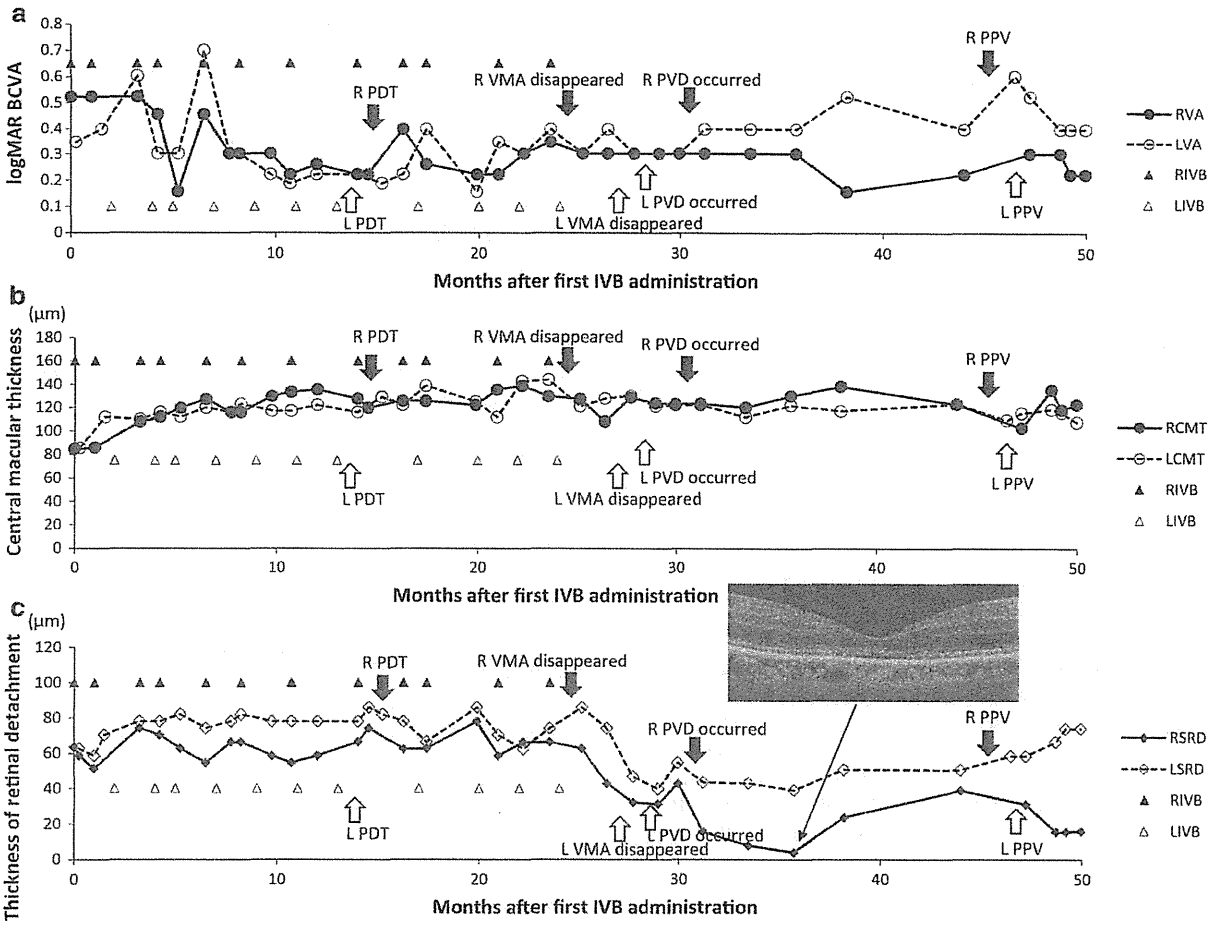

Fig. 4 LogMAR BCVA, CMT, and SRD changes and OCT scans after the first administration of IVB. The patient received 23 alternate administrations of IVB in both eyes; 12 times in the right eye and 11 times in the left eye. He also received half-fluence photodynamic therapy in both eyes. Two years after the first administration of IVB, when a partial PVD occurred, the vitreomacular adhesion had disappeared. Around this time, SRD improved, and IVB was therefore discontinued. Complete PVD was noted a few months later. Four years after the first administration of IVB, he sought treatment to eliminate myodesopsia and underwent pars plana vitrectomy. **a** LogMAR BCVA improved slightly while receiving IVB treatment. **b** CMT increased while receiving IVB treatment. **c** Reduced SRD was noted after PVD occurrence

Discussion

Although OCT findings of OMD have revealed outer retinal structural abnormalities in the foveal areas [5–8], chronic subfoveal SRD has never been reported in patients with OMD. In our case, the patient had experienced subfoveal SRD for the past 5 years. Furthermore, the lack of remarkable findings in FA/ICGA (Fig. 1) and the poor response to RF-PDT [22, 23] suggested that our patient's diagnosis might not have been chronic CSC. The OCT findings of the right eye 3 years after the first IVB administration showed no apparent SRD, but discontinuous reflectivity of the IS/OS lines in the foveal area (Fig. 4). These OCT findings were consistent with those observed in OMD patients in other studies [8, 11]. Since cone photoreceptor density is highest in the foveal region [18, 19], the subfoveal SRD resulted in a decreased number of cone photoreceptor cells, explaining the patient's central visual field defects (Fig. 3), loss of visual acuity, and reduced multifocal ERG responses (Fig. 2b).

Recently, the term "foveal cavitation," a subfoveal optical gap in SD-OCT, has been reported in patients with achromatopsia, cone dystrophy, and autosomal recessive Stargardt disease [24–27]. Although foveal

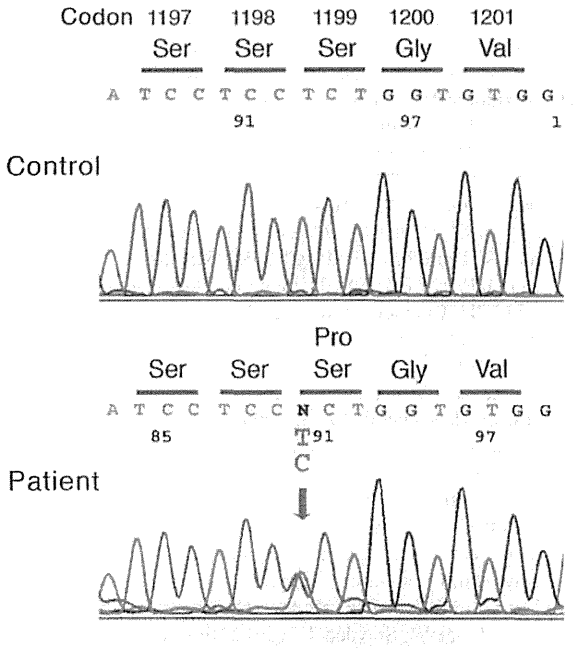

Fig. 5 Sequence analysis of exon 4 of the *RP1L1* gene. The *arrow* indicates the position of the substituted nucleotide (c.3595T>C in exon 4) which resulted in a heterozygous missense mutation (p.S1199P)

cavitation is similar to foveal retinal detachment seen in our patient, foveal cavitation is usually accompanied with the retinal pigment epithelium atrophy, becomes progressively worse, and at least does not disappear.

In eyes with PVD, the levels of various cytokines are thought to be lower than in eyes without PVD [28, 29], so SRD reduction might be caused by PVD occurrence. Otherwise, SRD reduction might also be caused by the disappearance of traction due to VMA disappearance or might be simply caused as a consequence of spontaneous atrophic changes. In the present case, logMAR BCVA correlated inversely with CMT, which increased after IVB treatment, suggesting that anti-vascular endothelial growth factor therapy thickened the outer retina by an unknown mechanism that improved BCVA.

Regarding *RP1L1* mutations, Kabuto et al. report an *RP1L1* missense mutation (p.S1199C) in a patient with a typical form of OMD [12]. Similarly, we identified a novel mutation (p.S1199P) at the same position. The serine residue (Ser1199) is highly conserved among *RP1L1* orthologs among other vertebrates [12], suggesting the functional importance of the serine residue in *RP1L1* protein, although no known domains or motifs have been identified in the region containing Ser1199.

In summary, we reported a single case of bilateral chronic subfoveal SRD in a patient with atypical OMD who carried a novel heterozygous *RP1L1* mutation (p.S1199P). The presence of the heterozygous mutation suggests autosomal dominant inheritance and will therefore be useful in genetic counseling. Moreover, our results further extend the phenotypic spectrum of *RP1L1*-associated OMD. The ophthalmologists should consider the possibility of OMD when they see the patients with chronic bilateral subfoveal fluid associated with normal FA/ICGA findings.

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Conflict of interest All authors declare no conflicts of interest. The authors have full control of all primary data, which will be made available for the journal to review upon request.

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Three-year visual outcome of photodynamic therapy plus intravitreal bevacizumab with or without subtenon triamcinolone acetonide injections for polypoidal choroidal vasculopathy

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ABSTRACT

Purpose To compare the 3-year visual outcome after double therapy of photodynamic therapy (PDT) with intravitreal bevacizumab (IVB) and triple therapy of PDT combined with IVB and subtenon triamcinolone acetonide (STTA) injections for polypoidal choroidal vasculopathy (PCV).

Design Retrospective, comparative, interventional case series.

Methods Medical records for 36 eyes in 36 patients (33 men, 3 women; mean age 73.5 years old; range 63–82 years old) with treatment-naive subfoveal PCV were reviewed retrospectively. Of the 36 eyes, 17 were treated with double therapy and 19 with triple therapy.

Results The change in visual acuity after triple therapy was significantly better than that after double therapy ($p<0.05$). At 36 months, improvement in visual acuity was seen in 5 eyes (29.4%) in the double therapy group and 10 eyes (52.6%) in the triple therapy group. Retreatment using the initial treatment was performed for six eyes (35.3%) in the double therapy group and five eyes (26.3%) in the triple therapy group, and treatment-free period was significantly longer in the triple therapy group ($p<0.05$). The mean number of additional antivascular endothelial growth factor therapy was higher in the double therapy group. Post-treatment vitreous haemorrhage or retinal pigment epithelium tear occurred only in the double therapy group, in one eye (5.9%) and one eye (5.9%), respectively.

Conclusions Initial therapy consisting of a single session of PDT combined with IVB and STTA improves vision in treatment-naive subfoveal PCV. Compared with double therapy, this triple therapy may be more effective for PCV.

INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) is a distinct clinical entity that differs from exudative age-related macular degeneration (AMD) in several ways. PCV is characterised by an abnormal branching vascular network with polypoidal terminal bulbs in the inner choroids.[1–4] The pathophysiology of PCV is unknown, but vascular endothelial growth factor (VEGF) and/or inflammation may be involved in the formation of PCV.[5–8] Therefore, anti-VEGF and anti-inflammatory therapy may be important for favourable clinical outcomes of PCV.

Photodynamic therapy (PDT) combined with intravitreal injections of bevacizumab (IVB) and triamcinolone acetonide (IVTA) has favourable effects on PCV.[9] In addition to the combined effect of PDT and IVB, the positive outcomes are attributed, at least in part, to IVTA inhibiting production of VEGF and vascular permeability and reducing choroidal inflammation after PDT. However, IVTA has risks of cataract progression, ocular hypertension and endophthalmitis. Subtenon injection of triamcinolone acetonide (STTA) may be useful as an alternative method, but the effect of STTA in combination therapy is unclear. Thus, the purpose of this study was to evaluate the 3-year visual outcomes in patients with PCV after triple therapy (standard-fluence PDT+IVB+STTA) and to compare these outcomes with those after double therapy (standard-fluence PDT+IVB).

METHODS

This study was performed as a retrospective, single-centre, non-randomised trial with the approval of the Institutional Review Board (IRB)/Ethics Committee at Jikei University. The study design adhered to the tenets of the Declaration of Helsinki and guidelines of the Japanese Ministry of Health, Labor, and Welfare. The subjects were 36 patients with treatment-naive subfoveal PCV who received PDT+IVB with or without STTA in our hospital from 1 January 2008 to 31 March 2009. All patients were Japanese, and their median age was 73.5 years old (range 63–82 years old). A clinical diagnosis of subfoveal PCV was established based on indocyanine green angiography (ICGA) findings of a network of vessels with a complex of branching vessels and multiple, terminal, reddish-orange, aneurysmal or polypoidal lesions. Patients were excluded if they had received previous treatment such as laser photocoagulation, submacular surgery and intravitreal bevacizumab injection (IVB); and if they had glaucoma, diabetic retinopathy or retinal vascular occlusion. Best-corrected visual acuity (BCVA) was measured with a Japanese standard decimal visual acuity chart and the mean BCVA was calculated using the logarithm of the minimum angle of resolution (logMAR) scale.

All patients underwent a standardised examination including slit-lamp biomicroscopy, fundus colour, fluorescein angiography (FA), ICGA with confocal scanning laser ophthalmoscopy (Heidelberg Retina Angiograph 2; Heidelberg Engineering, Heidelberg, Germany or Rodenstock Scanning Laser Ophthalmoscope Model 101;

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Rodenstock Instruments, Munich, Germany) and macular optical coherence tomography (OCT) using a Cirrus HD-OCT system (Carl Zeiss Meditec, Dublin, California, USA). FA was performed to determine the lesion type, location and choroidal neovascularisation (CNV) activity. ICGA was used to determine the presence and location of polypoidal lesions and branching vascular network vessels, and to determine the greatest linear dimension (GLD).

All patients had documented visual loss at baseline. The initial treatment included IVB injection plus ICGA-guided PDT 1 week after the injection, with or without subtenon injection of STTA (20 mg kenacort-A; Bristol-Myers Squibb, New York, New York, USA). Triamcinolone acetonide was injected with a dull, 23-gauge needle at the posterior subtenon space using a small incision at the conjunctival fornix of the inferotemporal side. IVB was injected 3.5–4.0 mm posterior to the corneal limbus into the vitreous cavity using a 30-gauge needle after topical anaesthesia was applied. PDT with the standard dose (6 mg/m^2) of verteporfin was administered according to the protocol of the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy study, except for the GLD. A 689-nm laser system (Carl Zeiss Meditec) was used to deliver 50 J/cm^2 of energy with an exposure time of 83 s. The GLD was measured based on ICGA findings to cover the polypoidal lesions and abnormal vascular network. The diameter of the laser spot size was calculated from the GLD plus 1 mm in all eyes. After the initial combined therapy of IVB and PDT with or without STTA, follow-up examinations including evaluation of OCT images were performed every 3 months until month 36. FA and ICGA were performed when new exudative changes or subretinal haemorrhages were seen on fundus examination or OCT. If polypoidal lesions were seen on ICGA, double or triple therapy was administered. For patients with residual or new exudative changes in branching vascular network vessels detected by ICGA, despite complete remission of polypoidal lesions, IVB or intravitreal ranibizumab injection (IVR) was administered. IVR was used from the first half of 2009. Additional injections were given based on OCT evidence of fluid at the macula, an increase in the central retinal thickness on OCT of at least 100 μm, a new macular haemorrhage or evidence of persistent fluid on OCT 1 month after the previous injection.

Statistical comparison for clinical variables was made using a Mann–Whitney U test for means with continuous data (eg, age) and the χ^2 test for categorical data (eg, gender). To compare the visual acuity at months 6, 12, 18, 24, 30 and 36, statistical analyses were performed using the Mann–Whitney test. The decimal BCVA obtained by the Landolt ring test was converted to the logMAR BCVA. A change in logMAR VA of ≥0.3 was taken to be a significant change. Comparisons were considered to be significant if the p value was <0.05. All analyses were carried out using Intercooled Stata V.7.0 (Stata Corporation, College Station, Texas, USA).

RESULTS

A total of 36 eyes with treatment-naive PCV were assessed in the study, of which 17 were treated with double therapy and 19 with triple therapy. The baseline characteristics of each group are shown in table 1. There were no significant differences in age, gender and baseline VA between the two groups.

The time courses of mean VA in the two groups are shown in table 2. The mean logMAR BCVAs in the double and triple therapy groups were 0.70±0.29 and 0.66±0.28, respectively, at baseline and 0.62±0.37 or 0.36±0.31, respectively, at 36 months. In the double therapy group, there was significant improvement of VA at only 18 months after treatment. In contrast, VA significantly improved after treatment in the triple therapy group and some improvement was maintained throughout the 3-year follow-up period. Outcomes at 36 months (figure 1) included improvement in VA in 5 eyes in the double therapy group and 10 eyes in the triple therapy group, and worsening of VA in two eyes in the double therapy group and one eye in the triple therapy group. BCVA improved by ≥0.3 logMAR, did not change significantly and decreased by ≥0.3 logMAR in 29.4%, 58.8% and 11.8% of eyes, respectively, in the double therapy group, and in 52.6%, 42.1% and 5.3% of eyes, respectively, in the triple therapy group.

In both groups, polypoidal lesions disappeared after treatment. At 36 months, there was complete disappearance of these lesions in 13 eyes in the double therapy group and 16 eyes in the triple therapy group. Retreatment details in the follow-up period are shown in table 3. The mean numbers of episodes of

Table 1 Baseline characteristics of 36 eyes of 36 patients with polypoidal choroidal vasculopathy

	Double therapy (n=17)	Triple therapy (n=19)	p Value
Gender			
Male, no. (%)	16 (94.1%)	17 (89.4%)	0.615
Female, no. (%)	1 (5.9%)	2 (10.6%)	
Age (years)			
Mean±SD	74.2±6.4	72.9±6.8	0.554
Baseline greatest linear dimension of lesion (μm)			
Mean±SD	3089±985	3534±1280	0.381
Baseline BCVA (logMAR)			
Mean±SD	0.70±0.29	0.66±0.28	0.537
RPED, no (%)	16 (94.1%)	18 (94.7%)	0.935
IRF or SRF (%)	11 (64.7%)	13 (68.4%)	0.813
SMH (%)	10 (58.8%)	11 (57.8%)	0.955
Type of polyps			
Single	4 (23.5%)	6 (31.5%)	0.590
Multiple	13 (76.5%)	13 (68.4%)	

BCVA, best-corrected visual acuity; IRF, intraretinal fluid; logMAR, logarithm of minimal angle of resolution; RPED, retinal pigment epithelium detachment; SMH, submacular haemorrhage; SRF, subretinal fluid.

Table 2 Mean best-corrected visual acuity in patients with polypoidal choroidal vasculopathy treated with double therapy or triple therapy during 36 months of follow-up

	Double therapy		Triple therapy		
Time from initial treatment (months)	BCVA (logMAR) (mean ±SD)	p Value (vs baseline)	BCVA (logMAR) (mean ±SD)	p Value (vs baseline)	p Value (double vs triple)
0	0.70±0.29		0.66±0.28		0.6989
6	0.48±0.38	0.0587	0.41±0.31	0.0185	0.7014
12	0.48±0.35	0.0628	0.39±0.35	0.0136	0.4735
18	0.45±0.36	0.0388	0.36±0.34	0.0052	0.4358
24	0.53±0.35	0.1218	0.36±0.30	0.0045	0.1640
30	0.56±0.36	0.1695	0.40±0.33	0.0175	0.2320
36	0.62±0.37	0.4240	0.36±0.31	0.0043	0.0429

BCVA, best-corrected visual acuity; logMAR, logarithm of minimal angle of resolution.

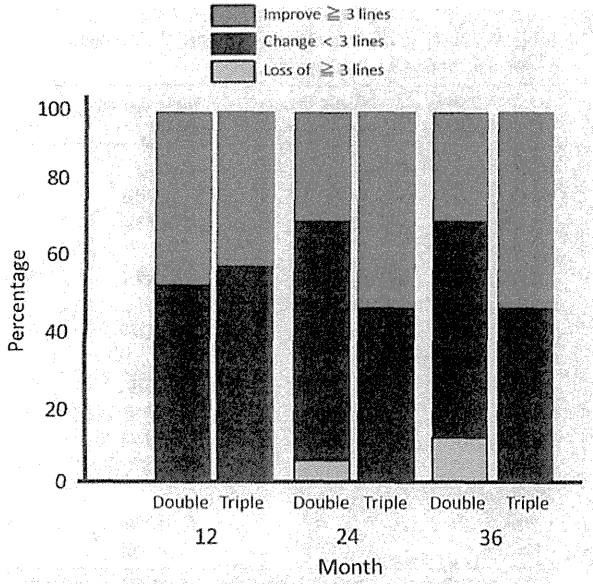

Figure 1 Change of best-corrected visual acuity (BCVA) in patients with polypoidal choroidal vasculopathy treated with double therapy or triple therapy during 36 months of follow-up. The rate of change in eyes with BCVA improvement of ≧3 lines, change <3 lines or loss ≧3 lines at 12, 24 and 36 months is shown.

PDT, injections of anti-VEGF agents and STTA over 36 months, including the initial regimen, were 1.35, 5.26 and 0.67, respectively, in the double therapy group, and 1.32, 3.95 and 1.21, respectively, in the triple therapy group. Although additional anti-VEGF agents were required in 14 eyes (100%) in the double therapy group and 14 eyes (73.7%) in the triple therapy group, retreatment using the initial treatment was performed for six eyes (35.3%) in the double therapy group and five eyes (26.3%) in the triple therapy group. Treatment-free period was longer in the triple therapy group compared with the double therapy group (24.4±8.7 vs 17.8±6.1 months, p=0.0373).

The adverse events during the follow-up period are shown in table 4. One eye developed submacular haemorrhage and one eye developed an retinal pigment epithelium (RPE) tear in the double therapy group during the study period, whereas no such complications occurred in the triple therapy group. No eye had ocular hypertension after STTA. Representative two cases with triple therapy are shown in figures 2 and 3, respectively.

DISCUSSION

The current study showed that triple therapy with IVB, STTA and PDT for treatment-naive subfoveal PCV maintained or improved visual acuity for 36 months after treatment without serious adverse events. The results suggest that this triple therapy can increase visual improvement obtained with the double therapy in treatment of PCV. Triple therapy may also reduce the number of required intravitreal anti-VEGF injections and extend treatment-free period compared with the double therapy.

Table 3 Number of treatments in patients with polypoidal choroidal vasculopathy treated with double therapy or triple therapy during 36 months of follow-up

	Double therapy (n=17)	Triple therapy (n=19)
Number of anti-VEGF injections, mean (SD)	5.26 (2.80)	3.95 (2.76)
Number of PDT, mean (SD)	1.35 (0.49)	1.32 (0.48)
Number of STTA, mean (SD)	0.67 (0.49)	1.21 (0.42)

PDT, photodynamic therapy; STTA, subtenon injection of triamcinolone acetonide; VEGF, vascular endothelial growth factor.

Table 4 Incidence of adverse events in patients with polypoidal choroidal vasculopathy treated with double therapy or triple therapy during 36 months of follow-up

Adverse events	Double therapy (n=17)	Triple therapy (n=19)
AMD-related adverse event		
Submacular haemorrhage	1 (5.9)	0
RPE tear	1 (5.9)	0
Subretinal fibrosis	4 (23.5)	3 (15.8)
Other ocular symptoms and signs		
Eye pain	4 (23.5)	4 (21.1)
Ocular hypertension	0	0
Eye irritation	5 (29.4)	6 (31.6)
Non-ocular adverse event		
Hypertension	2 (11.8)	1 (5.3)
Cardiovascular event	0	0

Values shown are number (%) of patients.
AMD, age-related macular degeneration; RPE, retinal pigment epithelium.

In previous studies, PDT has been shown to maintain or improve visual outcomes and resolve polypoidal lesions in PCV eye.[10–12] The Japanese Guidelines for PDT recommend PDT in patients with PCV.[13] However, long-term follow-up in patients with PCV after PDT has shown poor visual outcomes due to a high frequency of recurrent polypoidal lesions, with the conclusion that PDT causes enlargement and neovascular changes involving abnormal vascular networks due to ischaemia, inflammation and increased VEGF expression.[14–16] Therefore, treatment of PCV has recently shifted to combined therapy of PDT and anti-VEGF or anti-inflammatory therapy.[17–28]

Upregulation of VEGF occurs in the aqueous humour in active PCV and strong expression of VEGF is found in the RPE and vascular endothelial cells in PCV lesions.[6 8] Additionally, VEGF and pigment epithelium-derived factor (PEDF) may modulate formation of subfoveal fibrovascular membranes in PCV.[5 6] Thus, anti-VEGF is another treatment option for PCV. Previous studies indicated that IVB might reduce the leakage in PCV but was ineffective for regression of polyps.[17] Anti-VEGF can successfully control the exudative changes associated with polyp. However, repeated injections were required, and more than 30% of cases were refractory to anti-VEGF monotherapy.[25] Recently, it has been reported that IVR monotherapy deteriorated mean BCVA during long-term follow-up (0.68±0.43 at baseline; 0.78±0.53 at 36 months) and mean numbers of IVR were 11.45±7.81 during mean follow-up of 42.58±12.59.[29] The effectiveness of anti-VEGF may decrease during long-term follow-up, indicating a tachyphylaxis effect or increased resistance to anti-VEGF.[29 30]

There is growing evidence that combined PDT and anti-VEGF therapy is likely to be useful in PCV. Combined PDT and IVB has been evaluated in several Asian countries.[17–19 21–24 26–28] Sato *et al* found significant improvement of vision after 1 year of PDT and IVB; however, the significant effect diminished at 2 years of follow-up.[18] A similar outcome was found by Lee *et al*, with short-term improvement of visual acuity in patients with PCV after PDT and IVB, but decreased treatment efficacy with

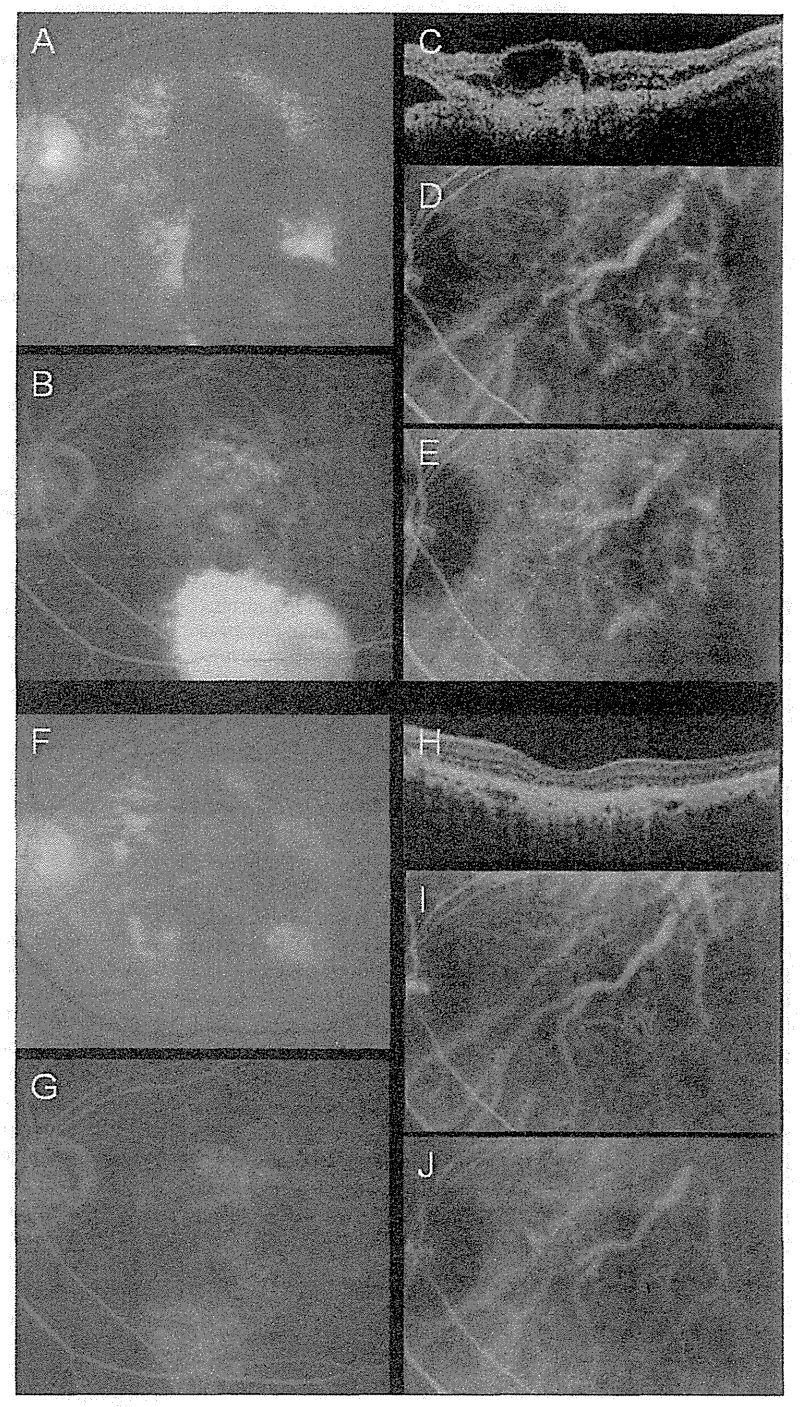

Figure 2 Fundus photograph, fluorescein angiography (FA), indocyanine green angiography (ICGA) and optical coherence tomography (OCT) findings before and at 12 months after triple therapy. (A) At baseline, fundus photograph demonstrates an orange-reddish nodule with thick exudates and with a subretinal haemorrhage. (B) FA shows hyperfluorescent leakage with retinal pigment epithelium (RPE) detachment at the inferotemporal macula. (C) OCT demonstrates RPE detachment, subretinal fluid and retinal oedema (D, early phase; E, late phase). ICGA shows a branching vascular network that terminates in polypoidal lesions. (F) At 12 months after triple therapy, fundus photograph shows absorption of the exudates. (G) FA demonstrates RPE window defect without leakage. (H) OCT reveals complete resolution of retinal oedema and subretinal fluid with disappearance of RPE detachment (I, early phase; J, late phase). ICGA shows regression of the polypoidal lesions.

time.[26] Thus, combined PDT and IVB for PCV may minimise the adverse effects of PDT and decrease the number of PDT or IVB treatments required, but a modified treatment strategy to enhance and maintain the initial efficacy seems to be required to improve long-term visual outcomes.

In the current study, we used double (PDT+IVB) or triple therapy (PDT+IVB+STTA) as an initial treatment strategy and IVB or IVR monotherapy as the major additional treatment approach. In previous studies, Terasaki *et al*[8] found clusters of dilated, thin-walled blood vessels surrounded by macrophages and fibrin material in two neovascular membranes obtained during macular translocation surgery for PCV, and Kikuchi *et al*[7] suggested that inflammatory processes are involved in the pathogenesis of PCV. Thus, inflammation may be a key element in the pathophysiology of PCV. Previous studies have shown that PDT combined with intravitreal injection of triamcinolone acetonide or STTA leads to improved visual acuity and lowers the rate of retreatment.[20] This may be associated with inhibitory effects of triamcinolone acetonide for inflammation at the choriocapillaris caused by irradiated laser beam. Luttrull and Spink