TABLE. Aqueous Humor Levels of the Inflammatory Mediators Before and After Intravitreal Injection of Triamcinolone Acetonide

Groups	Mediators	Control (n = 17) (pg/mL)	RRD (n = 19)		*P* Value	
			Baseline (pg/mL)	After IVTA (pg/mL)	C vs B	B vs I
Cytokines	IL-6	21 ± 23	261 ± 674	277 ± 617	<.001[a]	.27
	IFN-γ	5.4 ± 8.2	16.8 ± 12.7	22.9 ± 9.6	.003[a]	.04[b]
	TNF-α	4.0 ± 7.3	3.6 ± 2.9	4.9 ± 2.8	.02[a]	.02[b]
Chemokines	MCP-1	177 ± 26	1004 ± 667	591 ± 515	<.001[a]	<.001[b]
	MIP-1α	1.3 ± 2.9	0.14 ± 0.28	0.22 ± 0.28	.77	.21
	MIP-1β	11 ± 3.7	33.4 ± 16.7	22.2 ± 10.3	<.001[a]	.004[b]
	RANTES	2.8 ± 3.4	3.0 ± 2.4	5.9 ± 3.2	.48	.008[b]
	Eotaxin	0.0 ± 0.0	22.6 ± 18.7	35.0 ± 21.0	<.001[a]	.11
	IP-10	485 ± 491	2384 ± 2553	1936 ± 1856	<.001[a]	.04[b]
	IL-8	4.5 ± 2.9	21.6 ± 11.6	26.7 ± 16.8	<.001[a]	.20
Growth factors	VEGF	61 ± 25	123 ± 67	206 ± 117	.003[a]	<.001[b]
	bFGF	9.5 ± 8.8	11.9 ± 11.5	20.3 ± 11.5	.35	.009[b]
	G-CSF	1.9 ± 3.4	19.7 ± 38.9	97.2 ± 107.8	<.001[a]	<.001[b]
	GM-CSF	191 ± 37	212 ± 68	275 ± 59	.23	.001[b]
	PDGF-BB	3.8 ± 5.3	5.3 ± 3.9	9.4 ± 4.1	.06	.007[b]

B = RRD at baseline; bFGF = basic fibroblast growth factor; C = control; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; I = RRD after IVTA; IFN-γ = interferon γ; IL-6 = interleukin 6; IL-8 = interleukin 8; IP-10 = interferon gamma–induced protein 10; IVTA =intravitreral injection of triamcinolone acetonide; MCP-1 = monocyte chemotactic protein 1; MIP-1α = macrophage inflammatory protein 1α; MIP-1β = macrophage inflammatory protein 1β; PDGF-BB = platelet-derived growth factor BB; RANTES = regulated on activation, normal T cell expressed and secreted; RRD = rhegmatogenous retinal detachment; TNF-α = tumor necrosis factor α; VEGF = vascular endothelial growth factor.

[a]Mann-Whitney *U* test.

[b]Wilcoxon signed rank test.

Subjects were recruited from patients referred to the Surgical Retina Service of Tohoku University Hospital. Surgical intervention and follow-up were both performed at this clinic. Informed consent for both the treatment and participation in the research for this prospective study (University Hospital Medical Information Network; UMIN Study ID N.: UMIN000009418) was approved by the institutional review board of Tohoku University Graduate School of Medicine (Prot. N.2006-262, November 20, 2006). Informed consent for both the treatment and participation in the research was obtained from each patient and the research was conducted according to the provisions of the Declaration of Helsinki, 1995 (as revised in Edinburgh, 2000).

• **PATIENTS:** All patients had RRD and were studied in the period before 25GMIVS. The inclusion criterion was clinically detectable RRD. The exclusion criteria were prior vitreous surgery or IVTA, intravitreal anti–vascular endothelial growth factor (VEGF), ocular inflammation, and vitreoretinal or optic nerve diseases. Clinical and demographic characteristics were collected, including age, macular status, extent of RRD, number of retinal breaks, preoperative best-corrected visual acuity (BCVA), 1-month-postoperative BCVA, 6-month-postoperative BCVA, 1-month-postoperative foveal thickness (FT), and 6-month-postoperative FT. BCVA was measured with the Landolt C visual acuity chart, and the decimal acuities were converted to logarithms of the minimal angle of resolution (logMAR) units. The extent of the RRD was graded 1 to 4 according to the number of quadrants it covered.

• **INTERVENTION:** IVTA was performed in all patients 1 day before 25GMIVS. The TA (Kenacort-A; Bristol-Meyers Squibb, Tokyo, Japan) diluent was replaced with a balanced salt solution (BSS Plus; Alcon Laboratories, Fort Worth, Texas, USA) after Millipore filtration (Millex GS Filter Unit with MF-Millipore MCE Membrane, 0.22 μm; Merck Millipore Ltd., Tullagreen, Carrigtwohill, County Cork, Ireland), and the volume was adjusted so that 0.1 mL contained 4 mg TA. The TA was injected using a 27-gauge needle and a standard pars plana approach (3.5 mm posterior to the limbus). Before performing IVTA, samples of the aqueous humor were collected and the levels of mediators in the anterior chamber were measured. We next performed IVTA, and a day later collected a second aqueous humor sample, before beginning 25GMIVS. During 25GMIVS, we also collected samples of the vitreous. Patients undergoing 25GMIVS for epiretinal membrane (ERM) or macular hole (MH) served as controls.

• **MAIN OUTCOME MEASURE:** We investigated mediator levels in the pre- and post-IVTA aqueous humor, as well as the relationship between mediator levels and clinical findings

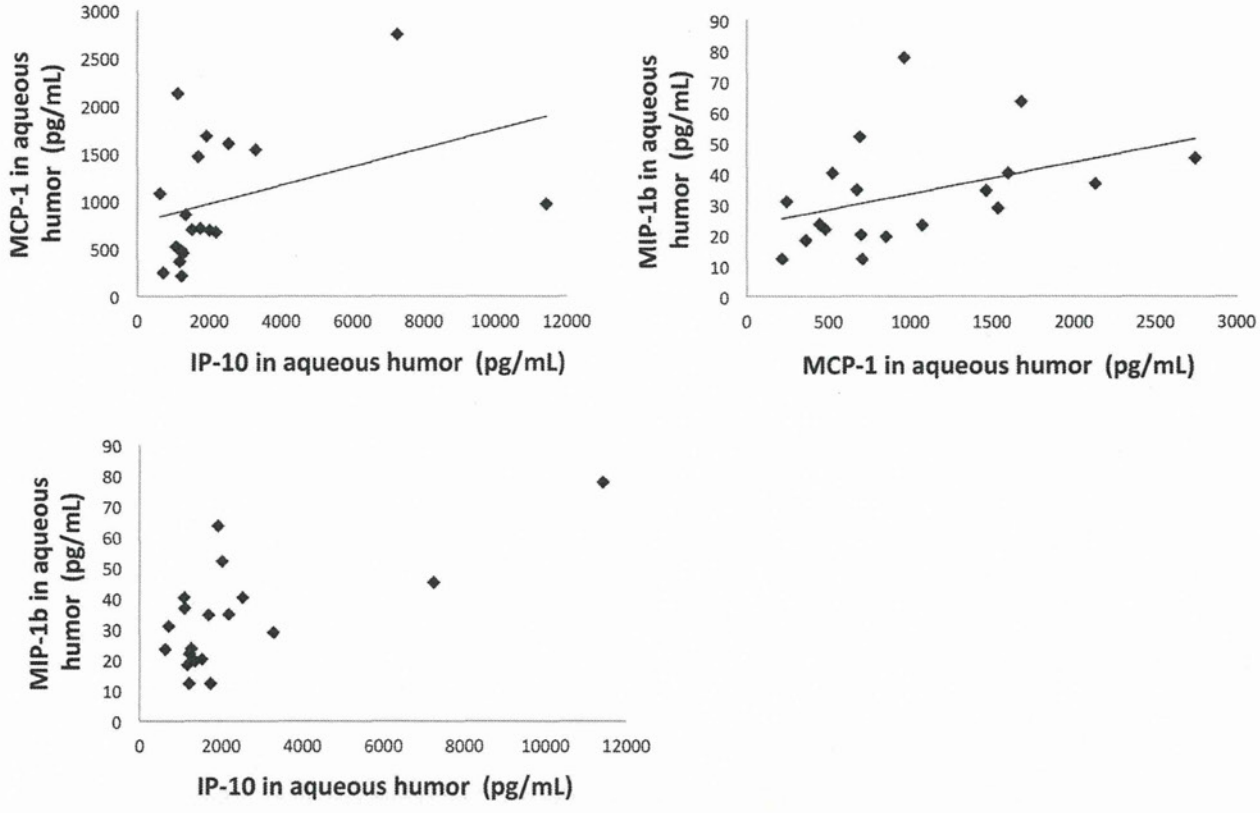

FIGURE 1. Relationship between chemokine levels in the aqueous humor before intravitreal injection of triamcinolone acetonide. (Top left) The aqueous humor level of monocyte chemotactic protein 1 (MCP-1) was significantly correlated with that of interferon γ–induced protein 10 (IP-10) ($r = 0.48$, $P = .04$). (Top right) In addition, the aqueous humor level of MCP-1 was significantly correlated with that of macrophage inflammatory protein 1β (MIP-1β) ($r = 0.50$, $P = .03$). (Bottom) The aqueous humor level of IP-10 was likely correlated with that of MIP-1β, but not significantly ($r = 0.44$, $P = .06$).

including age, macular status, size of RRD, number of retinal tears, preoperative BCVA, 1-month-postoperative BCVA, 6-month-postoperative BCVA, 1-month-postoperative FT, and 6-month-postoperative FT. We also measured mediator levels in the post-IVTA vitreous.

• MEASUREMENT OF INFLAMMATORY MEDIATORS: We withdrew aqueous humor samples before IVTA with a 30-gauge needle, to prevent increasing intraocular pressure later on, after IVTA. We next collected aqueous humor samples 1 day after IVTA, just before 25GMIVS. Special care was taken to avoid touching intraocular tissues (ie, the cornea, the iris, and the lens) and to prevent mixing intraocular samples with other fluids. The samples of aqueous humor (about 100 μL) were collected in sterile tubes and were immediately frozen at −80 C. Control samples of the aqueous humor from eyes undergoing vitreous surgery for ERM or MH were collected as controls and were also immediately frozen. The inflammatory mediators we investigated fell into 3 groups: (1) 3 cytokines: interleukin 6 (IL-6), interferon γ (IFN-γ), and TNF-α; (2) 7 chemokines: MCP-1/CCL2; macrophage inflammatory protein 1α (MIP-1α)/CCL3; macrophage inflammatory protein 1β (MIP-1β)/CCL4; regulated on activation, normal T cell expressed and secreted (RANTES)/CCL5; eotaxin/CCL11; interferon γ–induced protein 10 (IP-10)/CXCL10; and IL-8/CXCL8; and (3) 5 growth factors: VEGF, basic fibroblast growth factor (bFGF), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and platelet-derived growth factor BB (PDGF-BB). Samples were analyzed using a multiplex bead analysis system, the Bio-Plex system (Bio-Rad Laboratories, Hercules, California, USA). A custom-made kit (Bio-Plex Human Cytokine Assay; Bio-Rad Laboratories) was used to detect the mediators. For the experiment, aqueous humor and vitreous samples were diluted 4 times with sample diluent (Bio-Rad Laboratories). A total volume of 50 μL from each sample was used for the assay. The kits were used according to the manufacturer's instructions.

• STATISTICAL ANALYSES: All analyses were performed with Ekuseru-Toukei 2006 software (Social Survey Research Information Co Ltd, Tokyo, Japan). The data

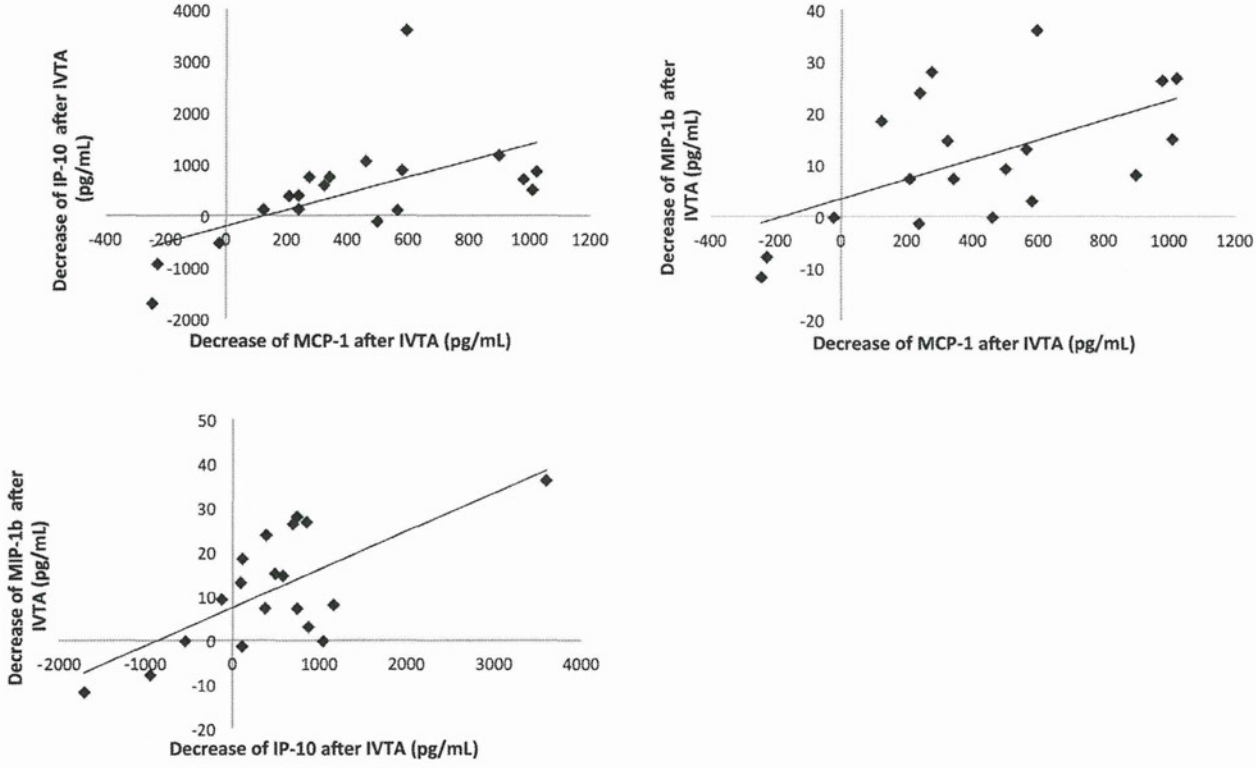

FIGURE 2. Alterations of levels of chemokines in the aqueous humor after intravitreal injection of triamcinolone acetonide. After intravitreal injection of triamcinolone acetonide (IVTA), the aqueous humor levels of monocyte chemotactic protein 1 (MCP-1), macrophage inflammatory protein 1β (MIP-1β), and interferon γ–induced protein 10 (IP-10) were significantly reduced ($P < .001$, $P = .004$, and $P = .04$, respectively). Each mediator showed a correlated decrease with the others (Top left: MCP-1 and IP-10: $r = 0.69$, $P = .001$; Top right: MCP-1 and MIP-1β: $r = 0.57$, $P = .01$; Bottom: IP-10 and MIP-1β: $r = 0.47$, $P = .04$).

are presented as means ± standard deviation. The significance of the difference between the pre- and post-IVTA data was assessed by the Wilcoxon signed rank test. The significance of the difference in the concentration of cytokines between eyes with an RRD and control subjects was assessed by the Mann-Whitney *U* test. The Spearman coefficient of correlation by rank was calculated to determine the correlation between aqueous humor and vitreous levels of the mediators. The Spearman coefficient of correlation by rank was also calculated to determine the correlation between the cytokine levels in the aqueous humor and clinical findings. The significance of the difference in the concentration of the cytokines between eyes with a macula-off RRD and macula-on RRD was assessed by the Mann-Whitney *U* test. A *P* value of less than .05 was considered to be statistically significant.

RESULTS

NINETEEN EYES OF 19 PATIENTS (15 MEN AND 4 WOMEN) WITH RRD were included in this study. The ages of the patients ranged from 40 to 71 years with a mean of 56.9 ± 8.0 years. Preoperative BCVA was 0.50 ± 0.75 logMAR units and ranged from −0.08 to 2.00 logMAR units. One-month-postoperative BCVA was 0.27 ± 0.40 logMAR units and ranged from −0.08 to 1.22 logMAR units. Six-month-postoperative BCVA was 0.11 ± 0.23 logMAR units and ranged from −0.08 to 0.70 logMAR units. One-month-postoperative BCVA and 6-month-postoperative BCVA were better than preoperative BCVA ($P = .06$ and $P = .04$, respectively). One-month-postoperative FT was 232.7 ± 42.4 μm and ranged from 156 to 306 μm. Six-month-postoperative FT was 246.1 ± 37.1 μm and ranged from 170 to 300 μm. The mean follow-up period was 7.3 ± 3.5 months with a range of 2 to 13 months. There were 11 eyes with macula-off RRD and 8 eyes with macula-on RRD. The extent of the RRD was 1.8 ± 0.5 and ranged from 1 to 3. The mean number of retinal tears was 2.1 ± 1.8. Complete reattachment was finally obtained in all 19 eyes with RRD after surgical intervention following IVTA. No severe adverse events such as endophthalmitis or any systemic side effects were observed in the study. Seventeen patients, including 9 with an ERM and 8 with an MH, were studied as controls.

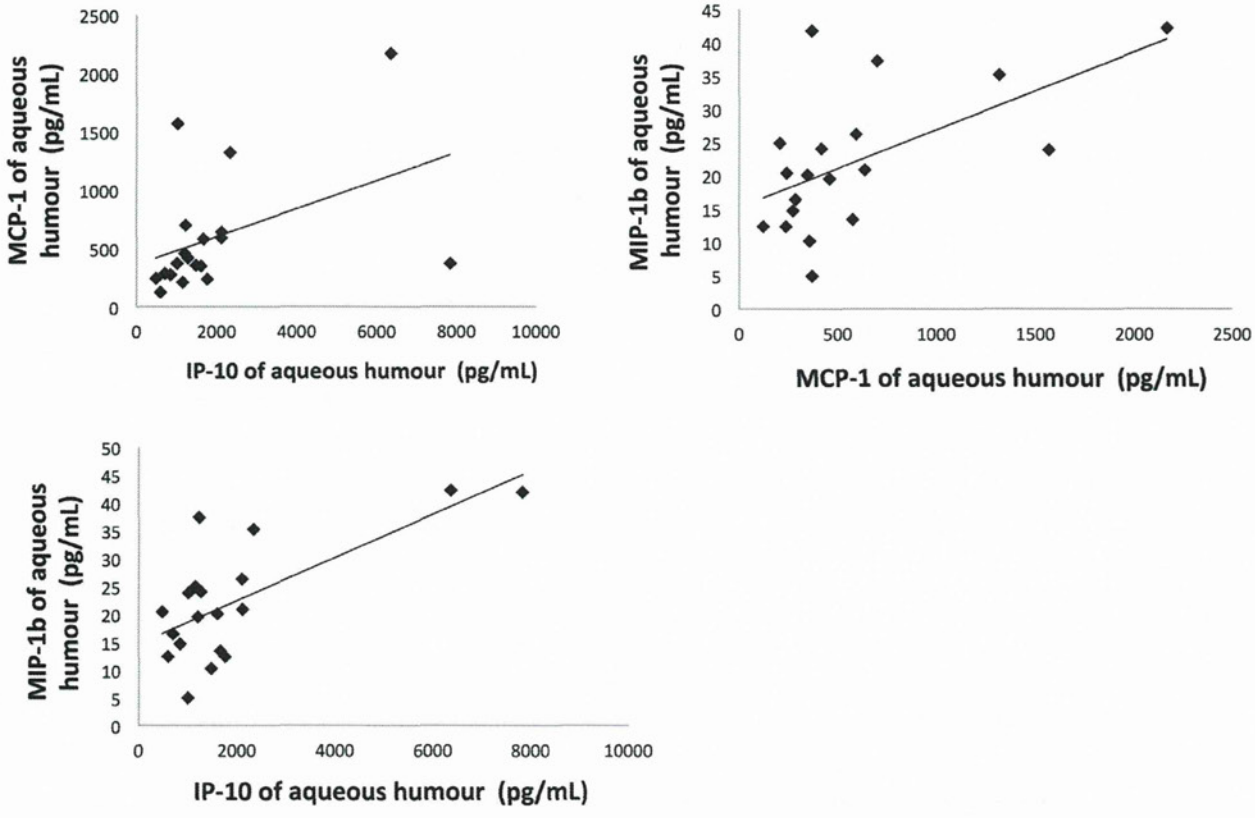

FIGURE 3. Relationship between chemokine levels in the aqueous humor after intravitreal injection of triamcinolone acetonide. (Top left) After intravitreal injection of triamcinolone acetonide, the aqueous humor level of monocyte chemotactic protein 1 (MCP-1) was significantly correlated with that of interferon γ–induced protein 10 (IP-10) ($r = 0.55$, $P = .01$). (Top right) In addition, the aqueous humor level of MCP-1 was significantly correlated with that of macrophage inflammatory protein 1β (MIP-1β) ($r = 0.56$, $P = .01$). (Bottom) The aqueous humor level of IP-10 was also significantly correlated with that of MIP-1β ($r = 0.49$, $P = .03$).

At baseline, IL-6, IFN-γ, MCP-1, MIP-1β, eotaxin, IP-10, IL-8, VEGF, and G-CSF were detected in the aqueous and were significantly higher in eyes with an RRD than in controls ($P < .001$, $P = .003$, $P < .001$, $P < .001$, $P < .001$, $P < .001$, $P < .001$, $P = .003$, $P < .001$, respectively) (Table). Before IVTA, the aqueous humor level of MCP-1 was significantly correlated with that of IP-10 ($r = 0.48$, $P = .04$) (Figure 1, Top left). In addition, the aqueous humor level of MCP-1 was also significantly correlated with that of MIP-1β ($r = 0.50$, $P = .03$) (Figure 1, Top right). The aqueous humor level of IP-10 was likely correlated with that of MIP-1β, but not significantly ($r = 0.44$, $P = .06$) (Figure 1, Bottom). After IVTA, the levels of MCP-1, MIP-1β, and IP-10 were significantly reduced ($P < .001$, $P = .004$, and $P = .04$, respectively) (Table). Each mediator showed a correlated decrease with the others, (MCP-1 and IP-10: $r = 0.69$, $P = .001$; MCP-1 and MIP-1β: $r = 0.57$, $P = .01$; IP-10 and MIP-1β: $r = 0.47$, $P = .04$) (Figure 2; Top left, Top right, and Bottom, respectively). After IVTA, the aqueous humor level of MCP-1 was significantly correlated with that of IP-10 ($r = 0.55$, $P = .01$) (Figure 3, Top left). In addition, the aqueous humor level of MCP-1 was significantly correlated with that of MIP-1β ($r = 0.56$, $P = .01$) (Figure 3, Top right). The aqueous humor level of IP-10 was also significantly correlated with that of MIP-1β ($r = 0.49$, $P = .03$) (Figure 3, Bottom). After IVTA, the vitreous level of MCP-1 was significantly correlated with the aqueous humor level of MCP-1 ($r = 0.52$, $P = .03$) (Figure 4, Top left). In addition, the vitreous level of IP-10 was significantly correlated with the aqueous humor level of IP-10 ($r = 0.78$, $P < .001$) (Figure 4, Top right). The vitreous level of MIP-1β was significantly correlated with the aqueous humor level of MIP-1β ($r = 0.86$, $P < .001$) (Figure 4, Bottom). After IVTA, the vitreous level of MCP-1 was significantly correlated with that of IP-10 ($r = 0.71$, $P = .001$) (Figure 5, Top left). In addition, the vitreous level of IP-10 was significantly correlated with that of MIP-1β ($r = 0.58$, $P = .01$) (Figure 5, Top right). The vitreous level of MCP-1 was likely correlated with that of MIP-1β, but not significantly ($r = 0.41$, $P = .09$) (Figure 5, Bottom).

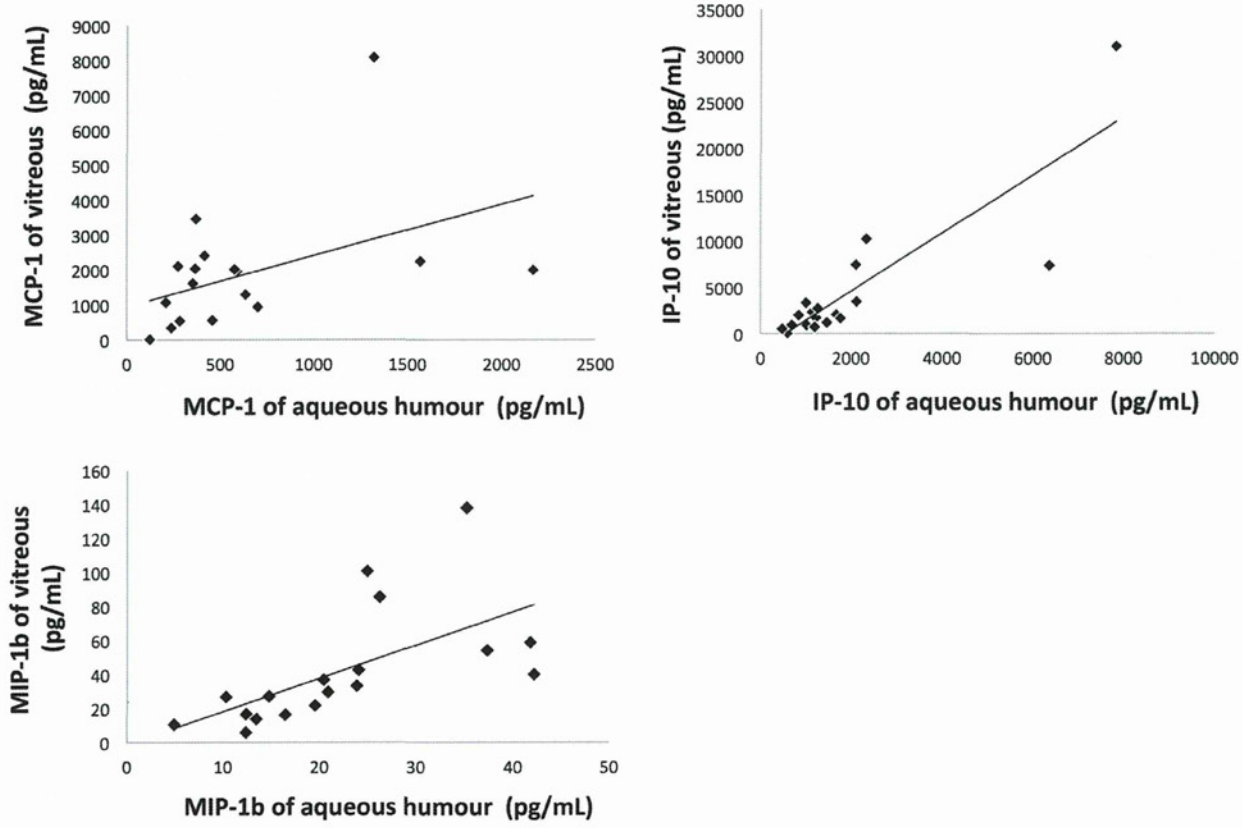

FIGURE 4. Relationship between chemokine levels in the aqueous humor and vitreous after intravitreal injection of triamcinolone acetonide. (Top left) After intravitreal injection of triamcinolone acetonide, the vitreous level of monocyte chemotactic protein 1 (MCP-1) was significantly correlated with the aqueous humor level of MCP-1 ($r = 0.52$, $P = .03$). (Top right) In addition, the vitreous level of interferon γ–induced protein 10 (IP-10) was significantly correlated with the aqueous humor level of IP-10 ($r = 0.78$, $P < .001$). (Bottom) The vitreous level of macrophage inflammatory protein 1β (MIP-1β) was significantly correlated with the aqueous humor level of MIP-1β ($r = 0.86$, $P < .001$).

Before IVTA, MCP-1 was higher in eyes with macula-off RRD (1337.2 ± 776.9 pg/mL) than in eyes with macula-on RRD (579.7 ± 256.8 pg/mL) ($P = .03$). IL-8 was also higher in eyes with macula-off RRD (27.4 ± 11.4 pg/mL) than in eyes with macula-on RRD (13.7 ± 7.4 pg/mL) ($P = .008$). Pre-IVTA eotaxin was significantly correlated with the extent of the RRD ($r = -0.60$, $P = .007$) and pre-IVTA VEGF was weakly correlated with the number of retinal tears ($r = 0.47$, $P = .04$). After IVTA, MCP-1 was higher in eyes with macula-off RRD (811.3 ± 609.2 pg/mL) than in eyes with macula-on RRD (288.5 ± 101.2 pg/mL) ($P = .006$). Post-IVTA IFN-γ and MIP-1α were significantly correlated with 1-month-postoperative BCVA ($r = 0.57$, $P = .01$ and $r = 0.66$, $P = .002$, respectively) and post-IVTA VEGF was also significantly correlated with the number of retinal tears ($r = 0.57$, $P = .01$). Post-IVTA bFGF was weakly correlated with 1-month-postoperative BCVA ($r = 0.47$, $P = .04$). Post-IVTA G-CSF was also weakly correlated with 6-month-postoperative FT ($r = -0.50$, $P = .049$).

DISCUSSION

WE SET OUT TO EVALUATE THE EFFECT OF IVTA ON mediator levels in the aqueous humor of human eyes with RRD. Our baseline measurements showed that levels of IL-6, IFN-γ, MCP-1, MIP-1β, eotaxin, IP-10, IL-8, VEGF, and G-CSF were significantly higher in eyes with RRD than in a control group. After IVTA, the levels of MCP-1, MIP-1β, and IP-10 decreased significantly; these decreases were closely correlated to each other. Thus, our study is the first to report IVTA's ability to suppress elevated levels of intraocular MCP-1, MIP-1β, and IP-10 in eyes with RRD (Figure 6). Our study additionally revealed that both before and after IVTA, MCP-1 was higher in eyes with macula-off RRD than in eyes with macula-on RRD.

Our finding that intraocular concentrations of MCP-1, IL-6, IL-8, and VEGF are significantly elevated in patients with RRD confirms existing research.[26–28] Our study also supports existing data showing that the intraocular concentration of TNF-α is not elevated in eyes with

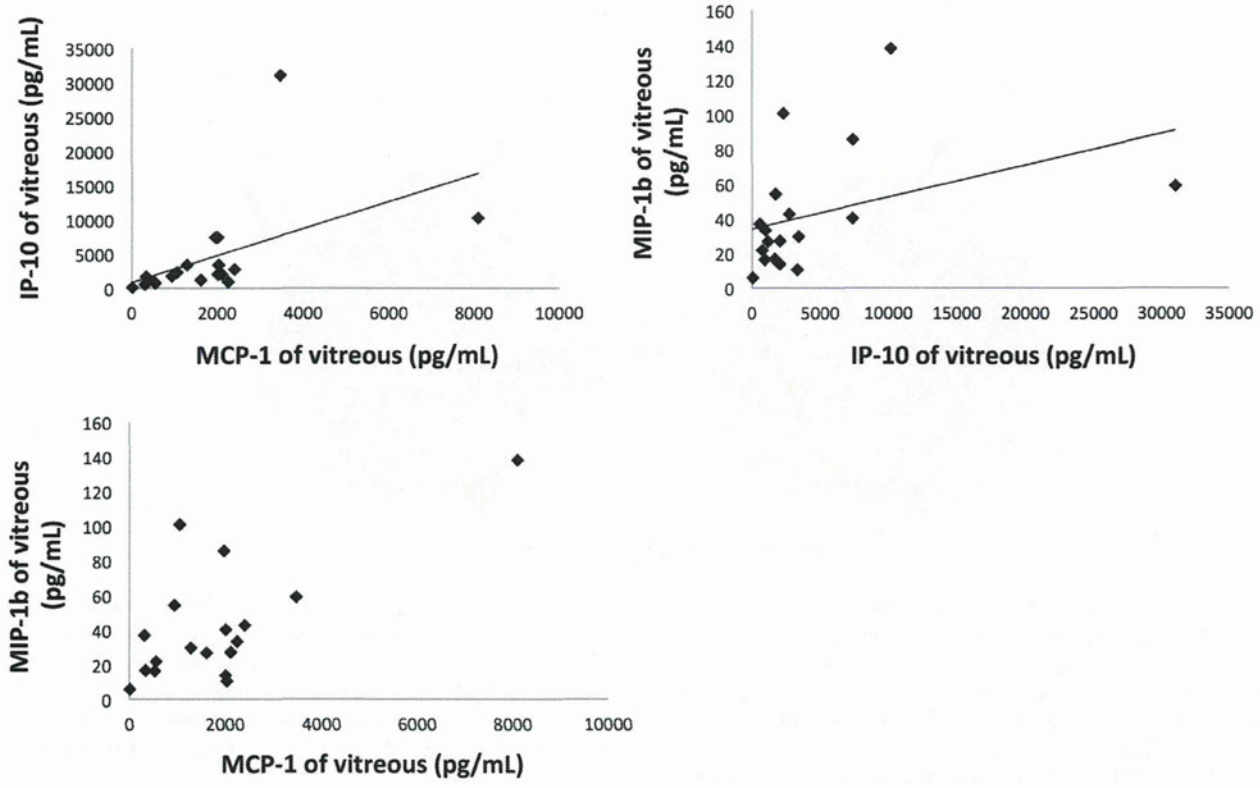

FIGURE 5. Relationship between chemokine levels in vitreous after intravitreal injection of triamcinolone acetonide. (Top left) After intravitreal injection of triamcinolone acetonide, the vitreous level of monocyte chemotactic protein 1 (MCP-1) was significantly correlated with that of interferon γ–induced protein 10 (IP-10) ($r = 0.71$, $P = .001$). (Top right) In addition, the vitreous level of IP-10 was significantly correlated with that of macrophage inflammatory protein 1β (MIP-1β) ($r = 0.58$, $P = .01$). (Bottom) The vitreous level of MCP-1 was likely correlated with that of MIP-1β, but not significantly ($r = 0.41$, $P = .09$).

RRD.[26] Interestingly, however, our data showed that corticosteroid cannot suppress TNF-α, contradicting our earlier work with an animal model.[14] The exact reason for this is unclear, but there were many differences between the earlier study and the present one besides the use of, respectively, animal and human subjects. The type of intraocular sample also differed (retinal in the animal study vs aqueous humor in the present one), as did the length of corticosteroid intervention (3 days vs 1 day), delivery method for the medication (intraperitoneal vs intravitreal injection), and method of analysis (mRNA quantification with RT-PCR vs protein quantification by multiplex bead analysis system).[14] Furthermore, it is also possible that the chemokines differ in their rate of clearance from the anterior chamber, and TNF-α might clear more slowly from the anterior chamber than MCP-1, MIP-1β, or IP-10.

The use of IVTA to treat eyes with proliferative ocular disease was part of a series of pioneering achievements in ophthalmology in the 1980s. Researchers at that time used animal models to show IVTA's capacity to inhibit fibroblast growth and significantly reduce the rate of retinal detachment.[29] Since then, it has become widely used in clinical practice in eyes with a broad range of retinal diseases, including uveitis, diabetic macular edema, retinal vein occlusion, and age-related macular degeneration.[20,21,23–25] Drug therapies in general have not yet been considered for eyes with RRD, as the priority has been improving methods for surgical reattachment. There are many patients, however, whose visual function does not recover completely, even after complete reattachment, because of retinal cell death in the time surrounding surgical intervention. Now that excellent surgical techniques, such as 25GMIVS, have established a very high reattachment rate,[1–10] the time has come to consider methods to address this gap in treatment.

We believe that IVTA, if performed promptly, can suppress photoreceptor apoptosis between RRD diagnosis and surgical intervention. The key to retinal protection during this period, as shown by initial studies using animal models, is control of the levels of several intraocular mediators, including MCP-1 and TNF-α.[14–16] These studies reported that the application of corticosteroid achieved this control for MCP-1, lowering its intraocular expression and suppressing photoreceptor death. We are the first to further demonstrate that the application of corticosteroid also reduces MCP-1 in human eyes with RRD. This is an

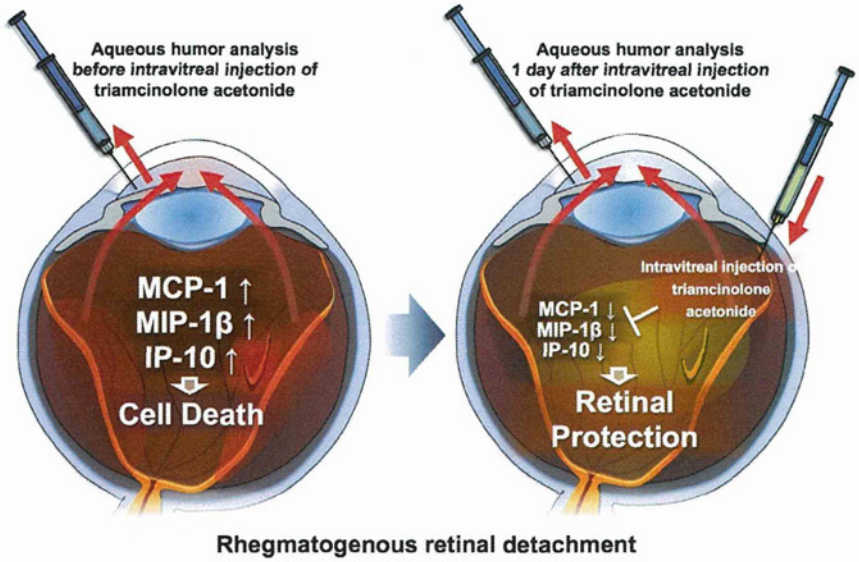

FIGURE 6. Schema of the protective effect of intravitreal injection of triamcinolone acetonide (IVTA) on retinal photoreceptors in eyes with rhegmatogenous retinal detachment. There was a relationship between intraocular chemokine levels before and after IVTA in eyes with rhegmatogenous retinal detachment. (Left) At the baseline, monocyte chemotactic protein 1 (MCP-1), macrophage inflammatory protein 1β (MIP-1β), and interferon γ–induced protein 10 (IP-10) were significantly higher in eyes with RRD than in controls. (Right) After IVTA, levels of MCP-1, MIP-1β, and IP-10 were significantly reduced, and these decreases were closely correlated to each other. Using IVTA, it was possible to suppress elevated levels of the critical intraocular chemokines (ie, MCP-1, MIP-1β, and IP-10) that lead to photoreceptor apoptosis.

important finding, because if the interval between RRD diagnosis and surgery is long, significant apoptosis can occur. This interval can vary depending on individual clinics, standards of care in different countries, and patients' lives.[30,31] Our results showed that MCP-1 levels were more elevated in eyes with macula-off RRD, a particularly relevant finding given that this type of RRD is known to lead to severe central visual disturbance postoperatively. The nature of IVTA means that it is especially appropriate if buckling is chosen as an RRD therapy, because that procedure keeps the entire vitreous intact in the eye. The injected corticosteroid can thus continue to suppress apoptosis even after surgery. In short, then, although it may not be possible to restore photoreceptors that have already undergone apoptosis, we believe that IVTA can help ensure the survival of the remaining photoreceptors.

The precise relationship between MCP-1, MIP-1β, and IP-10, and their role in apoptosis in eyes with RRD, remains unclear. As we have already reported, the first of these controllable mediators, MCP-1, exhibits increased expression in animal models in the Muller glia and macrophage/microglia.[14–16] MCP-1 can contribute to monocyte recruitment in areas where the outer retina has detached during the pathogenesis of RRD. The second mediator, MIP-1β, is a member of the C-C subfamily of chemokines, like MCP-1. Recent animal studies showed that MIP-1β is the most upregulated chemokine, and that it is involved in the recruitment of bone marrow–derived monocyte lineage cells to the hypoxic retina.[32,33] Since RRD causes hypoxia in the detached area of the outer retina, it is thus understandable that MIP-1β levels rise. MIP-1β is also upregulated in human eyes with macular edema associated with branch retinal vein occlusion, and is significantly reduced after IVTA.[34] In this clinical study, a decrease in foveal thickness after IVTA was directly correlated with a decrease in MIP-1β.[34] Thus, it may not be surprising that MCP-1 and MIP-1β were expressed in eyes with RRD, as RRD leads to retinal ischemia and inflammation. The third mediator, IP-10, belongs to the group of α-chemokines. It has been reported to be significantly associated with increased levels of MCP-1 in vitreous samples from patients with RRD and proliferative diabetic retinopathy.[35] The relationship between these 3 upregulated and controllable chemokines, however, remains unclear, and should be the subject of future research. If their antibodies were injected in animal eyes with RRD and the response analyzed, the chemokines' pathway and order of expression could be clarified. Although it may be impossible to detect caspase 3 activity in the aqueous humor or vitreous, it should be possible in the retina.[36] A more direct assay of apoptosis, therefore, such as an anti–cleaved caspase 3 test, might also demonstrate that retinal apoptosis is regulated after IVTA, clearly confirming our hypothesis.

Our study was thus limited by the lack of a direct assay of apoptosis, as well as a small sample size, an interval between administration of IVTA and analysis of its effects that was

necessarily short because of ethical considerations, and a lack of clinical, morphologic, and functional findings from a comparison between an IVTA group and a non-IVTA group. Nevertheless, we believe our results show that IVTA is currently the best way to suppress intraocular mediators and reduce photoreceptor death in eyes with RRD, at least until the antibodies for these mediators are ready for clinical use.

In conclusion, our findings show that elevated MCP-1, MIP-1β, and IP-10 in human eyes with RRD can be controlled with the application of IVTA. The decreases after IVTA in MCP-1, MIP-1β, and IP-10 were closely correlated to each other. Preconditioning with IVTA suppressed levels of intraocular MCP-1, MIP-1β, and IP-10, chemokines that, when elevated, can lead to photoreceptor apoptosis in eyes with RRD. Further investigation is needed to evaluate the relationship between these chemokines and clinical findings of postoperative visual quality and complications to determine the efficacy of IVTA.

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Biosketch

Hiroshi Kunikata was born in the city of Oita in Oita prefecture, Japan, and grew up in the city of Hitachi in Ibaraki prefecture. He graduated from the School of Medicine at Tohoku University, Sendai, Japan and received his PhD from the same institution. He is currently an Associate Professor of Ophthalmology at the Tohoku University Graduate School of Medicine, and vice-Chairman of the Department of Ophthalmology at Tohoku University Hospital. His primary research interests are vitreoretinal surgery and neural protection.

ARTICLE

Efficacy of combined 25-gauge microincision vitrectomy, intraocular lens implantation, and posterior capsulotomy

Naoko Aizawa, MD, Hiroshi Kunikata, MD, PhD, Toshiaki Abe, MD, PhD, Toru Nakazawa, MD, PhD

PURPOSE: To evaluate the efficacy of combined 25-gauge microincision vitrectomy surgery, intraocular lens (IOL) implantation, and posterior capsulotomy.

SETTING: Department of Ophthalmology, Tohoku University Graduate School of Medicine, Sendai, Japan.

DESIGN: Comparative case series.

METHOD: The medical records of eyes that had 25-gauge microincision vitrectomy and IOL implantation without posterior capsulotomy (June 2009 to May 2010) or with posterior capsulotomy (June 2010 to May 2011) were reviewed. Outcomes measured were corrected distance visual acuity (CDVA) at 1 and 6 months, the rate of neodymium:YAG (Nd:YAG) laser capsulotomies for postoperative posterior capsule opacification (PCO), and the rate of surgical complications.

RESULTS: The records of 343 eyes were reviewed; 136 eyes did not have a posterior capsulotomy, and 207 eyes had a posterior capsulotomy. There was a significant difference in the rate of Nd:YAG capsulotomy between the no-capsulotomy group (18 eyes, 13.2%) and the capsulotomy group (2 eyes, 1.0%) ($P<.01$). The mean CDVA improved postoperatively in both groups ($P<.01$); in 20 patients with postoperative PCO, the mean CDVA improved after Nd:YAG capsulotomy ($P<.05$). Intraoperatively, gas leaked into the anterior chamber in 5 (6.3%) of 79 eyes in the capsulotomy group that required fluid–air exchange.

CONCLUSIONS: Combined 25-gauge microincision vitrectomy, IOL implantation, and posterior capsulotomy was safe and reduced the need for postoperative Nd:YAG capsulotomy. Posterior capsulotomy should be performed with caution in eyes that are expected to require intraoperative fluid–air exchange.

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The most common postoperative complication of combined phacoemulsification and vitrectomy (ie, phacovitrectomy) is posterior capsule opacification (PCO).[1,2] Posterior capsule opacification can lead to a gradual decrease in the quality of vision and visual acuity postoperatively. It has been reported that in general, the PCO rates are lower with 23-gauge transconjunctival phacovitrectomy than with 20-gauge phacovitrectomy.[2] The 25-gauge microincision vitrectomy technique was first reported in 2002.[3,4] Although 10 years have passed, the PCO rate after 25-gauge microincision phacovitrectomy has not been determined.

PCO after intraocular lens (IOL) implantation often requires additional treatment with a neodymium:YAG (Nd:YAG) laser. Postoperative Nd:YAG laser capsulotomy is efficient and safe; however, it can cause severe complications, such as retinal detachment, cystoid macular edema, glaucoma, and luxated IOLs.[5–8] In addition, some cases of PCO cannot be treated with Nd:YAG capsulotomy and surgical intervention is required.[9] Thus, it would be desirable to establish a new technique for reducing or eliminating PCO after phacovitrectomy. A recent study[10] evaluated a technique for primary posterior capsulotomy using a 25-gauge vitreous cutter to prevent PCO in

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patients with vitreoretinal disease who require phacovitrectomy. The study found this technique completely prevented PCO formation during a 12-month follow-up. We believe the new technique is efficient and have used it in almost all our phacovitrectomy surgeries since we adopted it. However, to our knowledge (PubMed search), the advantages and disadvantages of 25-gauge microincision vitrectomy with posterior capsulotomy have not been discussed or reported, although this technique would benefit many patients with retinal disease.

The purpose of this study was to evaluate the efficacy of combined 25-gauge microincision vitrectomy, IOL implantation, and posterior capsulotomy in more than 300 patients.

PATIENTS AND METHODS

This retrospective analysis comprised the medical records of eyes that had pars plana vitrectomy (PPV) using a 25-gauge trocar cannula system. The study evaluated eyes that had PPV combined with IOL implantation before posterior capsulotomy was added to the surgery (June 2009 to May 2010) (no-capsulotomy group) and eyes that had combined PPV and IOL implantation after posterior capsulotomy was added to the surgery (June 2010 to May 2011) (capsulotomy group). After receiving an explanation of the purpose and procedures of the surgery, all patients provided informed consent. This study conformed to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the School of Medicine, Tohoku University.

Surgical Technique

The same surgeon (H.K.) performed all vitrectomies at Tohoku University Hospital. The surgeries were performed with retrobulbar anesthesia and the oblique sclerotomy technique using the Accurus Vitrectomy System (Alcon Laboratories, Inc.). First, an infusion cannula was inserted through the inferotemporal sclera; this was followed by insertion of 2 cannulas through the superotemporal and superonasal sites. Next, before the vitrectomy, a 2.4 mm superotemporal corneal incision was created and phacoemulsification, aspiration, and IOL implantation were performed. The posterior capsule was then removed from the center toward the periphery using a 25-gauge vitreous cutter and a pars plana approach, enabling removal of a well-centered posterior capsule with a diameter of approximately 5.0 mm.

Postoperative Protocol

All patients had a complete ocular examination at 6 months after surgery. The corrected distance visual acuity (CDVA) was measured using the Landolt C visual acuity chart; decimal acuities were converted to logMAR units. An Nd:YAG laser capsulotomy was performed when clinically indicated by the presence of PCO during the 6-month follow-up.

Statistical Analysis

The significance of the between-group differences in the patients' mean age, sex, and vitreoretinal disease was determined using the Mann-Whitney *U* test and chi-square for independence test. The significance of the differences in the rate of Nd:YAG capsulotomy performed postoperatively was determined by the Fisher exact probability test.

RESULTS

The records of 343 eyes were reviewed. The no-capsulotomy group comprised 136 eyes and the capsulotomy group, 207 eyes. Table 1 shows the patients' mean age and retinal diseases as well as the rate of postoperative Nd:YAG capsulotomy. The Nd:YAG capsulotomy rate was statistically significantly higher in the no-capsulotomy group than in the capsulotomy group ($P<.01$, Fisher exact probability test). There was no difference in the mean age or vitreoretinal diseases between the 2 groups ($P=.91$, Mann-Whitney *U* test, and $P=.61$, χ^2 for independence test, respectively).

The mean preoperative CDVA was statistically significantly better in the capsulotomy group (0.66 logMAR ± 0.60 [SD]) than in the no-capsulotomy group (0.86 ± 0.62 logMAR, $P<.01$, Mann-Whitney *U* test). The mean postoperative CDVA in the no-capsulotomy group (0.35 ± 0.47 logMAR) and the capsulotomy group (0.21 ± 0.39 logMAR) was statistically significantly better than the preoperative CDVA ($P<.01$, Wilcoxon signed-rank test).

Table 2 shows the characteristics, intraoperative details, and postoperative course of the 20 eyes with postoperative PCO requiring Nd:YAG capsulotomy. Of the 18 eyes in the no-capsulotomy group, 6 had epiretinal membrane (ERM), 1 had a macular hole, 7 had proliferative diabetic retinopathy (PDR), and 4 had rhegmatogenous retinal detachment (RRD). Of the 2 eyes in the capsulotomy group, 1 had ERM and 1 had RRD.

The mean time from the initial surgery to the Nd:YAG capsulotomy was 3.1 ± 2.2 months in the no-capsulotomy group and 4.5 ± 2.1 months in

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Table 1. Rate of postoperative Nd:YAG capsulotomy.

Group	Nd:YAG Rate, n (%)	Age		Retinal Disease (Number/%)
		Mean ± SD	Range	
No capsulotomy (n = 136)	18 (13.2)	64.4 ± 9.7	32, 90	ERM (48/35.3); MH (30/22.1); PDR (28/20.6); RRD (20/14.7); PVR (2/1.5); other (8/5.9)
Capsulotomy (n = 207)	2 (1.0)*	63.3 ± 11.2	21, 83	ERM (92/44.4); MH (34/16.4); PDR (33/14.5); RRD (28/13.5); PVR (3/1.4); other (17/8.2)

ERM = epiretinal membrane; IOL = intraocular lens; MH = macular hole; Nd:YAG = neodymium:YAG; PDR = proliferative diabetic retinopathy; PVR = proliferative vitreoretinopathy; RRD = rhegmatogenous retinal detachment
*$P<.01$, Fisher exact probability test

the capsulotomy group. In the 20 eyes with postoperative PCO, the mean CDVA was significantly better after Nd:YAG capsulotomy than before Nd:YAG capsulotomy (0.35 ± 0.36 logMAR versus 0.44 ± 0.35 logMAR; $P<.05$, Wilcoxon signed-rank test). Figure 1 shows a representative eye in the capsulotomy group that had no PCO postoperatively and 2 eyes in that group (eyes 19 and 20, Table 2) that developed postoperative PCO.

Table 2. Characteristics, intraoperative details, and postoperative course of eyes with postoperative PCO requiring Nd:YAG capsulotomy.

Eye	Age (Y)	Sex	Diagnosis	PCX	CDVA (logMAR)		
					Preop	Pre Nd:YAG	Post Nd:YAG
1	68	F	ERM	–	0.2	0.2	0.0
2	65	M	ERM	–	0.2	0.5	0.4
3	65	M	ERM	–	0.4	0.2	0.1
4	73	M	ERM	–	0.5	0.3	0.2
5	65	M	ERM	–	0.0	−0.1	−0.1
6	65	M	ERM	–	0.4	0.2	0.2
7	62	F	MH	–	1.1	0.5	0.7
8	55	F	PDR	–	0.3	0.4	0.7
9	48	M	PDR	–	1.2	0.7	0.3
10	69	M	PDR	–	1.1	0.5	0.4
11	69	M	PDR	–	0.8	1.0	0.4
12	69	M	PDR	–	0.4	0.2	0.1
13	73	M	PDR	–	0.5	1.0	1.0
14	60	M	PDR	–	1.1	1.0	1.0
15	68	F	RRD	–	1.3	0.0	−0.1
16	54	M	RRD	–	2.0	1.2	1.1
17	51	M	RRD	–	−0.08	0.2	0.0
18	64	M	RRD	–	0.0	0.2	0.2
19	73	F	ERM	+	0.3	0.2	0.2
20	60	M	RRD	+	0.1	0.4	0.1

CDVA = corrected distance visual acuity; ERM = epiretinal membrane; MH = macular hole; Nd:YAG = neodymium:YAG; PCO = posterior capsule opacification; PCX = posterior capsulotomy; PDR = proliferative diabetic retinopathy; RRD = rhegmatogenous retinal detachment

Six models of IOLs were implanted (Table 3). There was a statistically significant difference in the models of IOL used between the 2 groups ($P<.001$, χ^2 for independence test). However, the optics of all IOLs were acrylic.

Intraoperatively, gas leaked into the anterior chamber in 5 (6.3%) of the 79 eyes requiring fluid–air exchange in the capsulotomy group; no eye in the no-capsulotomy group had this complication ($P=.07$, Fisher exact probability test). There were no surgical complications such as IOL dislocation or subluxation associated with posterior capsulotomy.

DISCUSSION

We evaluated the efficacy of combined 25-gauge microincision vitrectomy, IOL implantation, and posterior capsulotomy. We found that the combined technique was practical and safe in eyes with vitreoretinal disease. There was a significant difference in the postoperative rate of Nd:YAG laser capsulotomy between the no-capsulotomy group and the capsulotomy group. The rate in the capsulotomy group (1.0%) was approximately 10 times lower than the rate in the no-capsulotomy group (13.2%).

Our study supports existing data showing that PCO occurs after phacovitrectomy, even when microincision vitrectomy surgery is performed in combination with cataract surgery.[2,11] Posterior capsule opacification is also reported to occur more frequently after phacovitrectomy (12.5%) than after phacoemulsification and IOL implantation alone (4.6%).[12] Our study also supports existing data showing that posterior capsulotomy is a practical method for preventing postoperative PCO in patients with vitreoretinal disease who require a phacovitrectomy.[10] However, our study also found that posterior capsulotomy did not prevent PCO in every case. Before we started this study, we could not speculate about the risk for postoperative PCO in the capsulotomy group. Because the posterior capsule was removed, we surmised that the lens

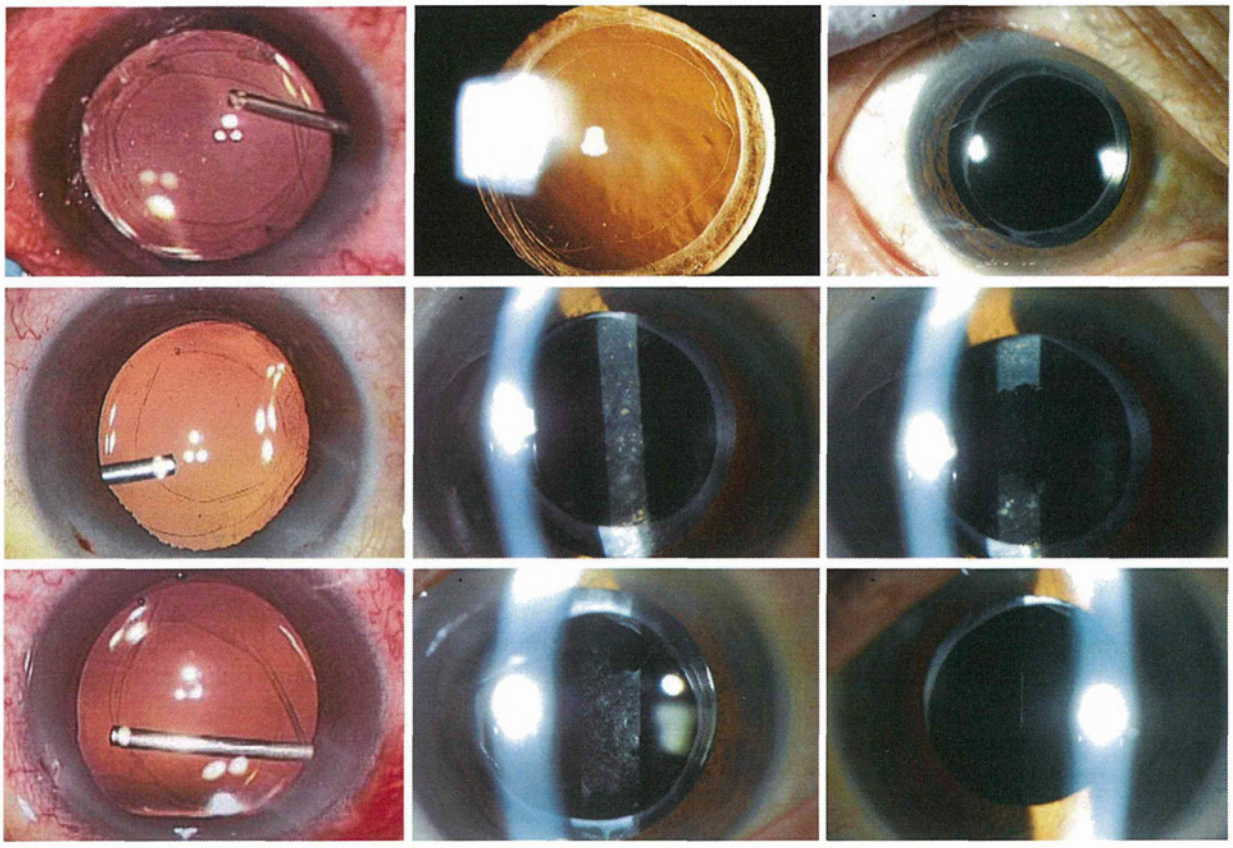

Figure 1. Clinical slit photographs of eyes after combined 25-gauge microincision vitrectomy, IOL implantation, and posterior capsulotomy. *Upper*: A 62-year-old woman with ERM. *Middle*: A 73-year-old woman with ERM (eye 19, Table 2). *Lower*: A 60-year-old man with RRD (eye 20, Table 2). *Left*: Intraoperative photographs of the anterior segment showing the center of the posterior capsule removed using a 25-gauge vitreous cutter. The posterior capsule is removed curvilinearly and completely. *Upper center*: Posterior capsule opacification was not detected in this eye 6 months postoperatively. *Middle and lower center*: Posterior capsule opacification was detected postoperatively. *Upper right*: Central optical zone was clear 6 months after the combined procedure. Neodymium:YAG laser was not used, and this photograph was taken at the same time as the *upper center*. *Middle and lower right*: Posterior capsule opacification was treated with an Nd:YAG laser capsulotomy, after which the central optical zone was clear.

epithelial cells (LECs) would have no scaffold to grow on, lacking the vitreous. However, the LECs grew onto the posterior surface of the IOL optic, albeit at a low rate (1.0%), even though the posterior capsule had been completely removed in the vitrectomized eye. Therefore, to further reduce the rate of PCO, posterior optic buttonholing might be added to the 25-gauge microincision vitrectomy with IOL implantation technique.[13,14] Postoperative PCO in both groups in our study was successfully treated with an Nd:YAG capsulotomy. In terms of pathology, there was no posterior lens capsule in the PCO in the capsulotomy group; thus, it should be described as retro-optical opacification.

Table 3. Intraocular lens models.

IOL Model	Eyes, n (%)	
	PCX−	PCX+*
Acrysof SN60WF (Alcon)	26 (19.1)	98 (47.3)
AF-1 PY60AD (Hoya)	87 (63.9)	0
AF-1 VA70AD (Hoya)	21 (15.4)	72 (34.8)
AF-1 iMics1 NY-60 (Hoya)	2 (1.5)	30 (14.5)
Eternity Natural NX-70 (Santen)	0	3 (1.4)
Tecnis ZCB00 (AMO)	0	4 (1.9)

IOL = intraocular lens; PCX = posterior capsulotomy
*$P<.001$, χ^2 for independence test

Both 25-gauge and 23-gauge microincision vitrectomy are commonly used throughout the world and are the most popular of the gauges for vitrectomy reported thus far.[15] Some patients ($\leq$1.0%) should have microincision vitrectomy surgery with caution.[16] However, the indication for 25-gauge microincision vitrectomy has expanded to various diseases, including PDR, RRD, giant retinal tear detachment, intraocular foreign body, and IOL dislocation,[17–25] because of the

quick visual recovery and significant reduction in postoperative astigmatism, conjunctival injection, pain, and discomfort.[26–28] In the past, the number of patients older than 45 years with retinal disease who had 20-gauge phacovitrectomy was high because if only vitrectomy were performed, the cataract would progress after surgery.[29] Thus, phacovitrectomy has 2 advantages. First, patients require 1 surgical intervention only. Second, lensectomy makes it possible for surgeons to easily remove the entire vitreous.[29] Although in some countries it is difficult to obtain medical insurance coverage for ophthalmic surgery, we believe that it is best to perform a single combined surgery in patients with retinal disease and preexisting cataract and in patients older than 50 years with retinal disease and clear lenses. We believe this because of the patient's expected quality of vision after phacovitrectomy and the minimal invasiveness of 25-gauge microincision vitrectomy. However, combined 25-gauge microincision vitrectomy and IOL implantation is still performed without posterior capsulotomy in most cases. There are thus 2 advantages to combining 25-gauge microincision vitrectomy and IOL implantation with posterior capsulotomy. First, a primary posterior capsulotomy technique using a 25-gauge vitreous cutter can prevent postoperative PCO, which can severely decrease CDVA in the affected eye. Second, posterior capsulotomy using a 25-gauge cutter can remove the fluid or residual ophthalmic viscosurgical device between the IOL and posterior capsule, making it possible for the posterior capsule to attach completely to the posterior surface of the IOL; this can prevent postoperative IOL rotation and postoperative temporary ocular hypertension. We believe this is especially beneficial when toric IOLs are used.

In our study, visualization was good for performing vitrectomies or peeling ERMs and internal limiting membranes. The 25-gauge instruments were clearly seen through the posterior-capsulotomized IOL when the vitreous cavity was filled with vitreous gel or an intraocular irrigating solution. However, in cases of fluid–air exchange, we had some difficulty seeing through the posterior-capsulotomized IOL and in removing the intraocular fluid and performing endophotocoagulation because the retrosurface of the IOL had an irregular reflex or there was dew in the fluid–air exchange. Although difficulty with visualization is mainly the surgeon's subjective impression and cannot be quantified, potential problems with visualization through gas when posterior capsulotomy is performed might be dependent on the IOL material and design. Six models of IOLs were implanted; however, the optic of each was acrylic. Further studies to quantify visualization difficulties might be required.

Furthermore, in approximately 6% of eyes in the capsulotomy group having fluid–air exchange, gas leaked into the anterior chamber; there was no leakage in the no-capsulotomy group. Thus, if an eye is expected to require fluid–air exchange, combined 25-gauge microincision vitrectomy, IOL implantation, and posterior capsulotomy should be performed cautiously or the posterior capsulotomy should be performed at the end of surgery, after the fluid–air exchange. Because posterior capsulotomy causes loss of the barrier between the anterior chamber and vitreous cavity, we were somewhat apprehensive about the risk for postoperative endophthalmitis. However, there were no postoperative complications, including endophthalmitis. Also, this technique should not be used in young patients with no cataract and active PDR or other ischemic retinal disease because we believe that rubeosis iridis or neovascular glaucoma could easily be induced by the lack of a posterior lens capsule.[30,31]

Our study had limitations; that is, it was retrospective and had a short follow-up (6 months). However, we believe that combined phacovitrectomy, IOL implantation, and posterior capsulotomy is the best approach to treating selected patients with retinal disease to maintain the highest quality of postoperative vision without additional interventions.

In conclusion, we found that combining 25-gauge microincision vitrectomy and IOL implantation with posterior capsulotomy was efficient, practical, and safe. Further studies are needed to evaluate postoperative visual quality and complications to determine the efficacy of the procedure.

WHAT WAS KNOWN

- The most common postoperative complication of phacovitrectomy is PCO. The 25-gauge microincision vitrectomy technique was first reported in 2002. Although 10 years have passed, the PCO rate after the procedure has not yet been determined.

WHAT THIS PAPER ADDS

- Combined 25-gauge microincision vitrectomy surgery, IOL implantation, and posterior capsulotomy was easily performed in phakic eyes with vitreoretinal disease, and leaving the IOL in rarely resulted in postoperative PCO.
- We believe that 25-gauge phacovitrectomy and IOL implantation with posterior capsulotomy is the best approach to treating selected patients to maintain the highest quality of postoperative vision without additional interventions.

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CASE REPORT

Choroidal excavation with polypoidal choroidal vasculopathy: a case report

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Purpose: This is a report of a case of choroidal excavation accompanied by polypoidal choroidal vasculopathy (PCV) and retinal pigment epithelium detachment (PED).

Methods: A 57-year-old Japanese woman who had begun complaining of metamorphopsia in her left eye 7 months earlier underwent spectral-domain optical coherence tomography (SD-OCT), fluorescein angiography (FA), and indocyanine green angiography (IA), as well as a routine ophthalmological examination.

Results: The patient's intraocular pressure, visual acuity, and visual field were within normal range. Ophthalmoscopy revealed a serous macular detachment, soft drusen, exudates, and a reddish-orange elevated lesion in the macula of the left eye. The right eye was normal. SD-OCT revealed two lesions in the left eye. One was a PED accompanied by a notch sign, and the other was a choroidal excavation. Additionally, FA revealed a window defect in the PED, and IA showed typical PCV. Three monthly injections of antivascular endothelial growth factor preserved visual acuity, but failed to have any visible effect on the lesion during the 6-month follow up period.

Conclusions: This is the first report of choroidal excavation accompanied by PED and PCV. The data suggest that choroidal excavation may be associated with various changes that have not been previously reported. Careful observation of such cases may therefore be necessary.

Keywords: choroidal excavation, polypoidal choroidal vasculopathy, anti-vascular endothelial growth factor treatment

Introduction

Choroidal excavation, an unusual structural change in the eye, has only recently been discovered thanks to advances in ocular imaging technology and the development of optical coherence tomography (OCT). The first report of choroidal excavations in the macula was made by Jampol et al in 2006,[1] who used time-domain (TD)-OCT. In 2010,[2] a report was published describing three more cases of choroidal excavation identified using spectral-domain (SD)-OCT, an imaging technique that enables a more detailed description of the morphology of choroidal excavation than TD-OCT.[3] In 2011, a series of 12 cases of choroidal excavation was documented,[4] including a case involving a young Japanese patient.[5] Choroidal excavation as a concept has thus come to be well defined.

The etiology of choroidal excavation, however, remains unclear, partly because the accepted belief has been that this type of lesion is stable and shows little change over time. A report by Wakabayashi et al, for instance, showed three cases of choroidal excavation with stable visual acuity over 6 months.[2] This stability seemed to indicate

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that choroidal excavation was simply the result of structural changes over a patient's lifetime. However, after finding a case of choroidal excavation accompanied by polypoidal choroidal vasculopathy (PCV), it was believed that choroidal excavation might become a platform for age-related macular degeneration (AMD) or an ischemic lesion such as choroidal neovascularization (CNV).

In this study, we report on the aforementioned case, in which the patient's choroidal excavation was accompanied by PCV and retinal pigment epithelium (RPE) detachment (PED). The expansion of this lesion led to a decrease in visual acuity during the follow-up period. As far as we know, this is the first report of a patient with choroidal excavation and PCV, so we will also discuss the possibility of ischemic change, as well as the treatments we attempted to administer.

Case report

A 57-year-old woman became aware of metamorphopsia in her left eye over a period of 7 months. The distortion gradually worsened, and she consulted a local ophthalmologist who found an abnormal macular lesion and referred her to our hospital. Her general family medical history and her personal medical history, including her history of ocular disease, were unremarkable.

Her best-corrected visual acuity (BCVA) was (1.2 × S-1.5 D, cyl-0.75 D, Ax80°) for the right eye and (1.0 × S-2.0 D, cyl-0.75 D, Ax90°) for the left eye at the time of her first visit. The intraocular pressure was 12 mmHg for both eyes. The anterior segment was normal in both eyes. The Humphrey Field Analyzer (HFA), with a 30-2 Swedish interactive threshold algorithm strategy (Carl Zeiss Meditec Inc, Dublin, CA), did not show any defects in either eye. The cup to disc ratio was 0.7 for the right eye and 0.8 for the left eye. The left fundus showed a small reddish-orange elevated lesion, drusen, exudates, and serous macular detachment in the macular area (Figure 1A). The right fundus showed nothing abnormal (Figure 1B).

Spectral-domain optical coherence tomography (SD-OCT) (Cirrus HD-OCT 4000; Carl Zeiss Meditec Inc) revealed PED with a notch sign, serous retinal detachment, and a choroidal excavation in the macular area of the left eye. The choroidal excavation, which was mainly located in the macula, continued into the PED. SD-OCT further revealed separation between the neural retina, the RPE, and the underlying layers (Figure 1C).

Conditions between the inner segment/outer segment (IS/OS) line and the nerve fiber layer seemed to be almost normal. However, there was a thinned RPE reflective line at the lesion, and we detected a notch sign, a constriction at the lower edge of the PED. We did not detect a double-layer sign, a highly reflective line seen between the RPE and the choroidal capillary layer. A highly-reflective lump was detected above the serous retinal detachment.

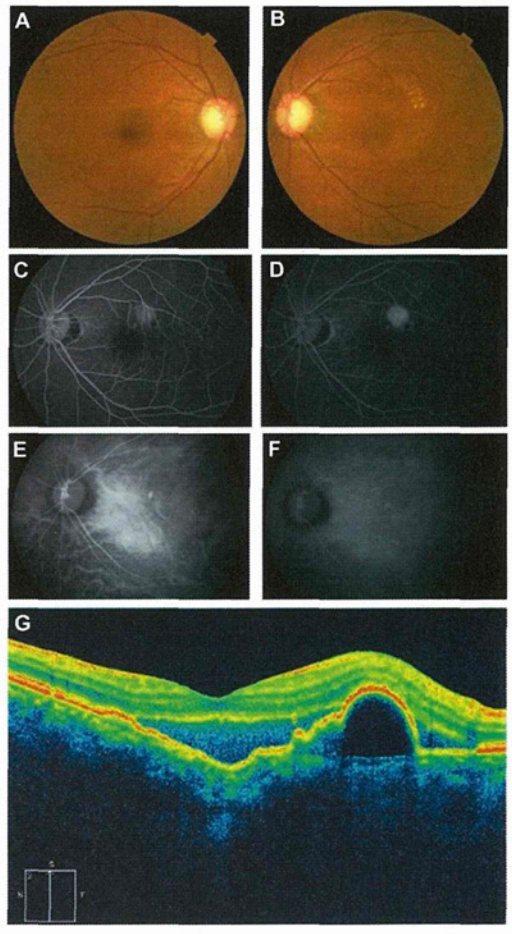

Figure 1 (**A** and **B**) show color fundus photographs of the right and left eyes, respectively. The left eye shows serous retinal detachment and exudates. (**C** and **D**) show the results of FA (early and late phase, respectively) and show hyperfluorescence (window defect) at the lesion of the PED. (**E** and **F**) show the results of IA (early and late phase, respectively) and show polypoidal fluorescence at the yellowish protruding lesion. SD-OCT demonstrates the separation of the retina between the inner segment and the outer segment junctions of the photoreceptor (IS/OS) line and the RPE with choroidal excavation (**G**).

Note: A protruding lesion was observed in the upper macular area, and PED ran along the upper part.

Abbreviations: FA, fluorescein angiography; PED, pigment epithelium detachment; SD-OCT, spectral-domain optical coherence tomography; IS/OS, inner segment/outer segment; IA, indocyanine green augiography; RPE, retinal pigment epithelium.

Fluorescein angiography (FA) (Figure 1D and E) revealed a window defect in the area of the PED, and indocyanine green angiography (IA) showed polypoidal hyperfluorescence in the early (Figure 1F) and late phases (Figure 1G). This lesion was coincident with the notch sign detected by OCT. The choroidal excavation lesion appeared unremarkable.

During successive follow up visits, the serous retinal detachment and exudates increased, and visual acuity gradually decreased. The patient received monthly intravitreal injections of antivascular endothelial growth factor (VEGF) (ranibizumab; 0.5 mg/0.05 ml) to treat the lesions for 3 months, but they did not react well during the first 2 months. Specifically, the serous retinal detachment and exudates increased (Figure 2D–F). However, improvement of the serous retinal detachment was observed after the third injection (Figure 2H and I), and her visual acuity remained at (0.8) at a follow-up visit 6 months later.

Discussion

The current study is a report on the case of a choroidal excavation accompanied by PCV and PED in the macula. Before this study, fewer than 20 cases of choroidal excavation were documented, and it was believed that the natural course of the disease was stable. Our discovery of a rare case of choroidal excavation associated with PCV contradicts this belief. Such a lesion may be resistant to anti-VEGF therapy, suggesting the importance of noting complications during the longitudinal follow-up period for patients with choroidal excavation.

The structural features of choroidal excavation have only recently been identified thanks to the improvements in image quality provided by OCT. Following the discovery that OCT could be used to detect the tissue microstructure of the human retina and coronary artery,[6] Fercher et al presented the first in vivo OCT images in 1993.[7] Many researchers now take advantage of the ever-progressing quality of the acquired images and of the software used to render those images. TD-OCT, an older technology, shows only unclear images of the relative position of the RPE in an optically clear space,[1] but SD-OCT can provide a clear image of a choroidal excavation. In our case, we used SD-OCT and were able to see the ELM and the IS/OS line very clearly.

In this case, the patient's BCVA was good, but she complained of metamorphopsia. We found a choroidal excavation comprising the layer from the RPE to the underlying choroid,

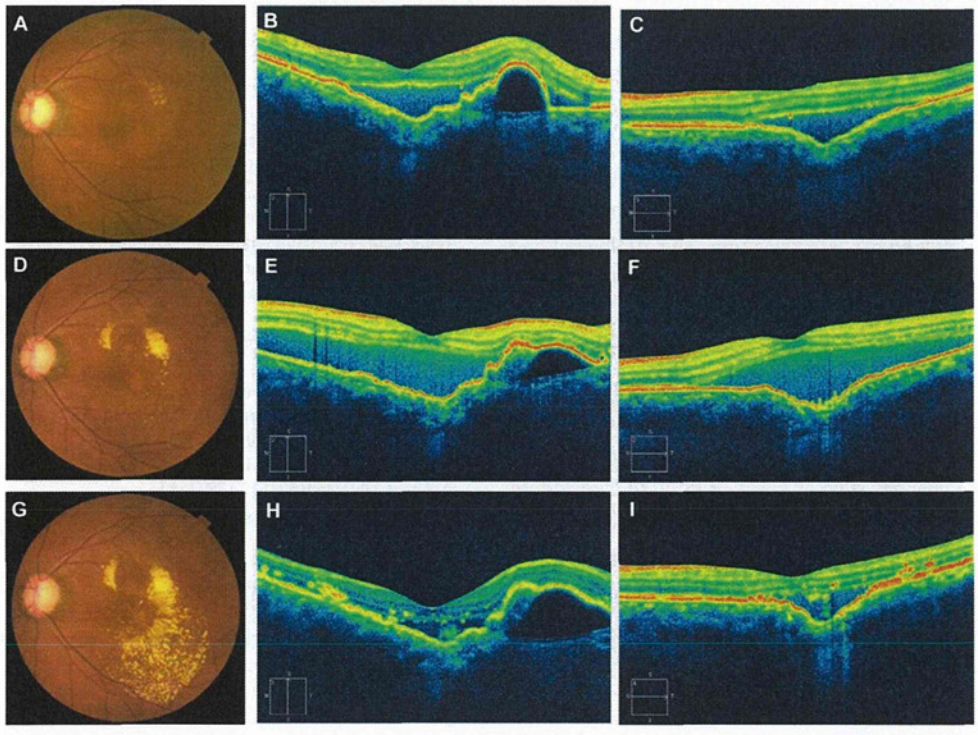

Figure 2 (**A–C**) are fundus photographs and OCT images before anti-VEGF treatment. (**D–F**) are fundus photographs and OCT images after initial anti-VEGF treatment. (**G–I**) are fundus photographs and OCT images after three rounds of anti-VEGF treatment. (**B**, **E** and **H**) are vertical OCT images and (**C**, **F** and **I**) are horizontal OCT images. The left eye shows serous retinal detachment and exudates (**A**). A choroidal excavation is located just inside the macular area. As described in Figure 1, the OCT images show the separation of the retina between the IS/OS line and the RPE (**B**). The horizontal image shows choroidal excavation more clearly than the vertical image (**C**). The left eye shows more exudates than that of her initial visit to us (**A**) (**D**) and an increase in serous retinal detachment (**E** and **F**). The retinal exudates increased after the 3 injections (**G**), but serous retinal detachment decreased (**H** and **I**).

Note: The extent of PED may have increased.

Abbreviations: OCT, optical coherence tomography; VEGF, vascular endothelial growth factor; IS/OS, inner segment/outer segment; RPE, retinal pigment epithelium; PED, pigment epithelium detachment.

including separation of the neural retina from the underlying RPE and choroid and localized to the area of the macula. The term "focal choroidal excavation" (FCE) may be a more appropriate representation of her condition.[2] There are two reported types of FCE; one is a conforming and the other a nonconforming lesion in the neural retina extending to the underlying excavated RPE and choroid. In our patient's case, the lesion was nonconforming.

Margolis et al have reported that the conforming type of lesion can become nonconforming when stress between the photoreceptor chips and the RPE gradually increases.[4] In our patient's case, there were also additional sources of stress, such as PED and the generation of PCV. Our patient also presented a thinned RPE reflective line, matching the report by Margolis.[4] In our patient, we were able to clearly see the ELM and IS/OS lines. In Margolis's report, these lines were faint. A clear IS/OS line is believed to be important for good visual acuity, so these results may explain the relatively good visual acuity our patient had when she consulted us.

Choroidal excavations can affect the structure of the RPE and the underlying choroidal layers over a lifetime, sometimes stimulating ischemic change followed by CNV[4] or PCV. Margolis has also suggested that such lesions might accompany ischemic changes.[4] Our patient had a choroidal excavation associated with CNV and PCV, but no ischemic change, causing us to believe that CNV and PCV arise not only from bad circulation, but also from a collapse of the Bruch membrane caused by a choroidal excavation. The etiological and pathological mechanism of choroidal excavations is not clear, nor is it clear whether they are congenital or acquired. Evidence is accumulating that suggests they may not be restricted unilaterally, as they do not show clear sex or race predilection. PCV following a choroidal excavation may be accidental. However, the possibility remains that FCE can be followed by devastating changes such as CNV or PCV, so care should be taken over the long term for patients with FCE.

The BCVA of our patient was over (0. 8), a prerequisite for treatment. Our first choice for treatment was a ranibizumab intravitreal injection, rather than photodynamic therapy (PDT), as we were following the Japanese guidelines for PDT.[8,9] Although the patient's visual acuity remained stable, a transient increase in serous retinal detachment and an increase in retinal exudates suggested it would be difficult to treat these kinds of lesions with anti-VEGF therapy. Had her BCVA declined, we would have been forced to revise her treatment to either PDT alone, or a combination of anti-VEGF therapy and PDT. Ischemic lesions accompanied by FCE may have a more complicated mechanism than that previously reported with respect to CNV and PCV. Although we are only presenting a case report, we might suggest that more attention should be paid to therapies for lesions in patients with FCE.

In conclusion, the value of this case report is that it presents information on the first known choroidal excavation associated with PCV. Our experience shows that choroidal excavations might be associated with different variable changes than have been previously reported. We believe that choroidal excavation may create circumstances leading to the generation of neovascularization and that there may be a need to reconsider the treatment of lesions associated with FCE in the future.

Disclosure

The authors report no conflicts of interest in this work.

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