The diagnosis of VKH disease was based on the appearance of bilateral uveitis associated with exudative retinal detachment. In all patients, secondary multiple leaks from the level of the RPE were seen during fluorescein angiography. The patients had no history of trauma or surgery. We ruled out the patients with lymphoma and other forms of uveitis. All patients were diagnosed as having the ocular findings of VKH disease with or without extraocular disorders. At the same time, we also diagnosed the patients according to the diagnostic criteria for VKH disease.[2] The diagnosis of complete VKH disease mandates the presence of neurologic and auditory findings and the integumentary signs. In case of no presence of the neurologic, auditory, or integumentary signs, we diagnosed probable VKH disease. In case of the presence of any of them, we diagnosed incomplete VKH disease.

The choroid was imaged by positioning the Heidelberg Spectralis instrument close enough to the eye to obtain an inverted image. The OCT instrument was centered on the eye such that the posterior pole image was not tilted. Each image was the product of 100 averaged scans. Using the software (version 1.5.12.0) with Heidelberg Spectralis OCT, the choroid was measured from the outer border of the hyperreflective line corresponding to the RPE to the inner scleral border. The subfoveal choroidal thickness in both vertical and horizontal sections (30° × 30°) through the center of the fovea was measured, and the average of the 2 was recorded. When choroidal thickness values become more than 1,000 μm, these are defined as a 1,000 μm because the inner scleral border could not be visualized by EDI-OCT. The height of retinal detachment at the fovea was also measured at the same time. The height of retinal detachment was defined as the distance between the outer surface of the neurosensory retina and the inner surface of the RPE. The reported measurements from OCT images represented the average of the horizontal and vertical measurements made by three co-authors (I.M., Y.S., and H.O.) who were masked to the treatment status. The results of the measurement of the choroidal thickness and the height of retinal detachment were analyzed using the Wilcoxon signed rank test.

Results

Sixteen eyes of 8 patients (3 men and 5 women; mean age, 36.4 years) with acute phase of VKH disease were evaluated. All patients visited within 1 month from the subjective onset during April and October in 2009. None of the patients had a history of either penetrating ocular trauma or surgery and all presented with subjective vision loss, headache, and mild fever. Six patients had meningismus with cerebrospinal fluid pleocytosis (Two additional cases of meningismus refused lumbar puncture.). Three patients had the perceptive hearing loss and another three patients had tinnitus. No cases showed any integumentary signs or any abnormality in their laboratory evaluation including the chest roentgenogram or serum angiotensin-converting enzyme levels. No eyes showed hyperemia of the conjunctiva, microphthalmia, and scleral thickening. Fifteen eyes had serous retinal detachment involving the fovea and multiple focal leaks at the level of RPE during fluorescein angiography. The remaining left eye of Patient 4 showed optic disk hyperemia and foveal striate secondary to papillitis without actual retinal detachment. All 16 eyes showed the leakage from the optic nerve head during fluorescein angiography, and patchy filling delay with indistinct choroidal vessels in indocyanine green angiography. We diagnosed all 8 cases as having the ocular findings of VKH disease

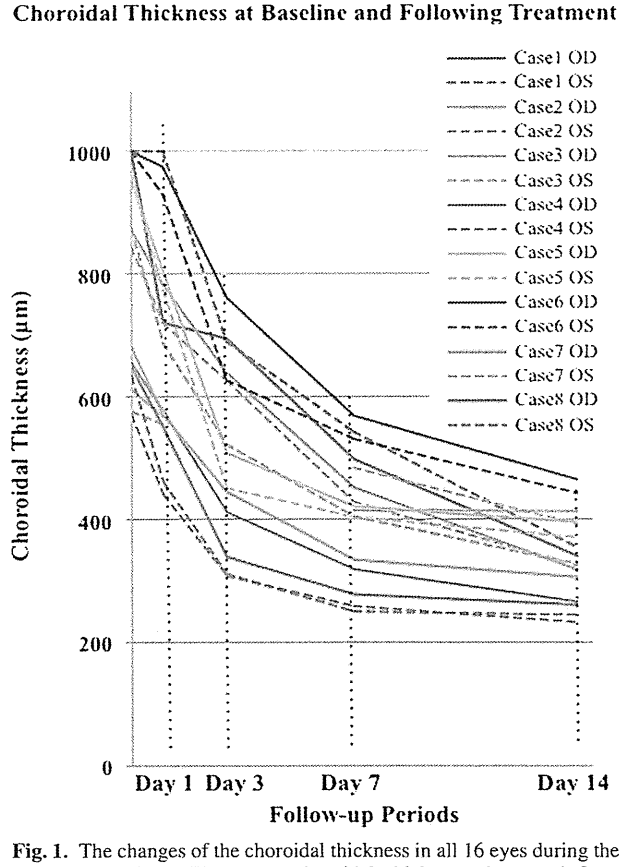

Fig. 1. The changes of the choroidal thickness in all 16 eyes during the follow-up periods. The mean choroidal thickness decreased from baseline to 86% at Day 1, 65% at Day 3, 51% at Day 7, and 42% at Day 14 of its original value.

(7 cases diagnosed as incomplete VKH and 1 case diagnosed as probable VKH). The left eye of Patient 4 was diagnosed as having the papillitis form of VKH disease. After the diagnosis, the patients were given 1,000 mg of intravenous methylprednisolone for 3 days followed by low-dose intravenous betamethasone or oral prednisolone or both.

The clinical changes of the choroidal thickness during the follow-up periods in all cases were summarized in Table 1 and Figure 1. Day 1, Day 3, and Day 14 were defined by the time intervals after initiation of the intravenous therapy. In both eyes of Patient 3, the choroidal thickness at Day 3 was not obtained. The serous retinal detachment resolved in 12 eyes by Day 14 and in all eyes by 1 month. The mean decimal BCVA levels improved from 0.71 (20/28) (0.15 logMAR) at baseline to 1.04 (20/19) (−0.02 logMAR) after resolution of serous retinal detachment ($P < 0.001$). Figures 2 and 3 were illustrated as the representative case with the ocular findings of VKH disease, and Figures 4 and 5 were illustrated as the representative case with the papillitis type of VKH disease.

The mean choroidal thickness in 16 eyes at baseline was 805 ± 173 μm, which decreased to 695 ± 175 μm at Day 1 ($P < 0.001$), 524 ± 151 μm by Day 3 ($P < 0.001$), and 341 ± 70 μm at Day 14 ($P < 0.001$). Choroidal thickness decreased during the course of treatment in all eyes. This corresponds to a percentage reduction from baseline of 14% at Day 1, 35% at Day 3, 49% at Day 7, and 58% at Day 14. The height of retinal detachment decreased from 408 ± 352 μm at baseline to 163 ± 133 μm at Day 3 ($P = 0.003$) and 10 ± 25 μm at Day 14 ($P < 0.001$), respectively.

Discussion

The choroidal thickness in patients with active onset VKH disease was much thicker than that reported for normal eyes[17] and the thickness dramatically

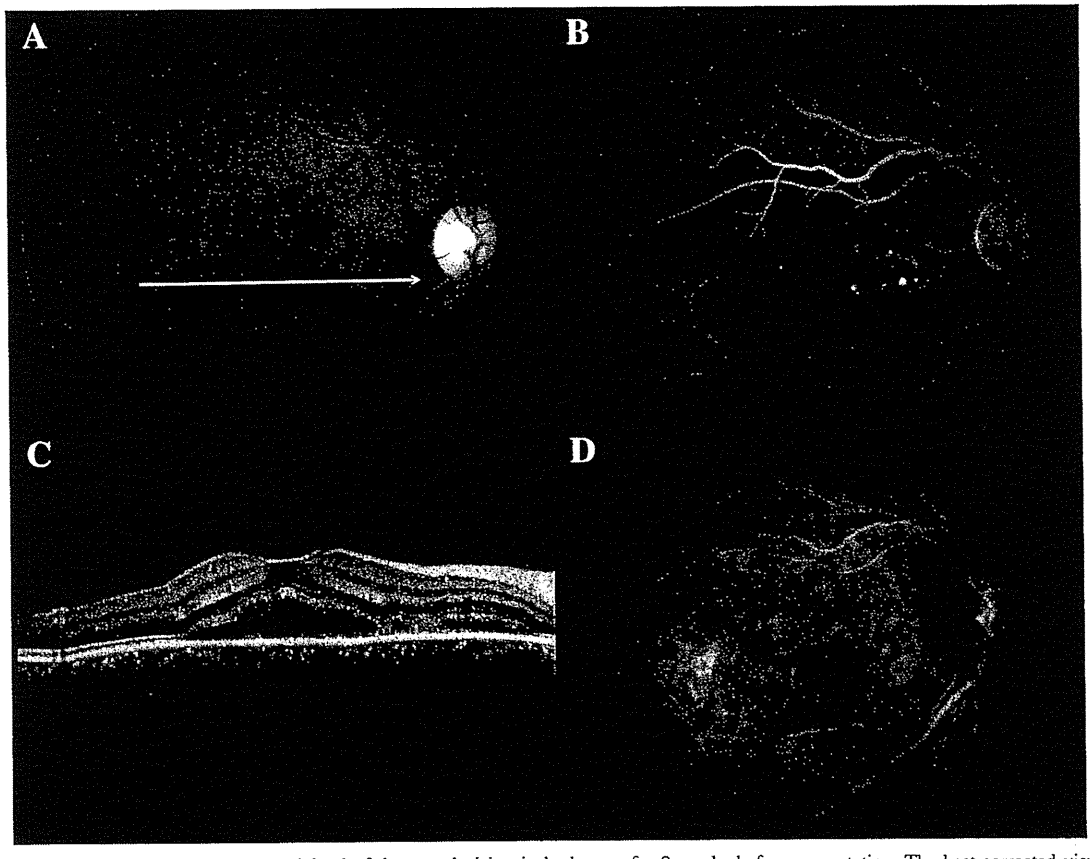

Fig. 2. Patient 8. A 35-year-old woman complained of decreased vision in both eyes for 2 weeks before presentation. The best-corrected visual acuity at baseline was 0.7 (20/29) (0.15 logMAR) in the right eye. **A.** Red-free fundus photography in the right eye showed a serous retinal detachment at baseline. **B.** Fluorescein angiography in the right eye showed multiple focal leaks and hyperfluorescence because of pooling in the subretinal space at baseline. **C.** Spectral-domain OCT in the right eye showed the serous retinal detachment of the macula and nasal to the macula. Spectral-domain OCT in the right eye (white arrow in fundus photograph) showed the serous retinal detachment of the macula and nasal to the macula. **D.** Indocyanine green angiography in the right eye showed patchy filling defects and the indistinct visualization of the choroidal vessels at baseline. She was diagnosed as having VKH disease. She was given intravenous methylprednisolone (1,000 mg, for 3 days) followed by tapered oral prednisolone starting at 40 mg/day.

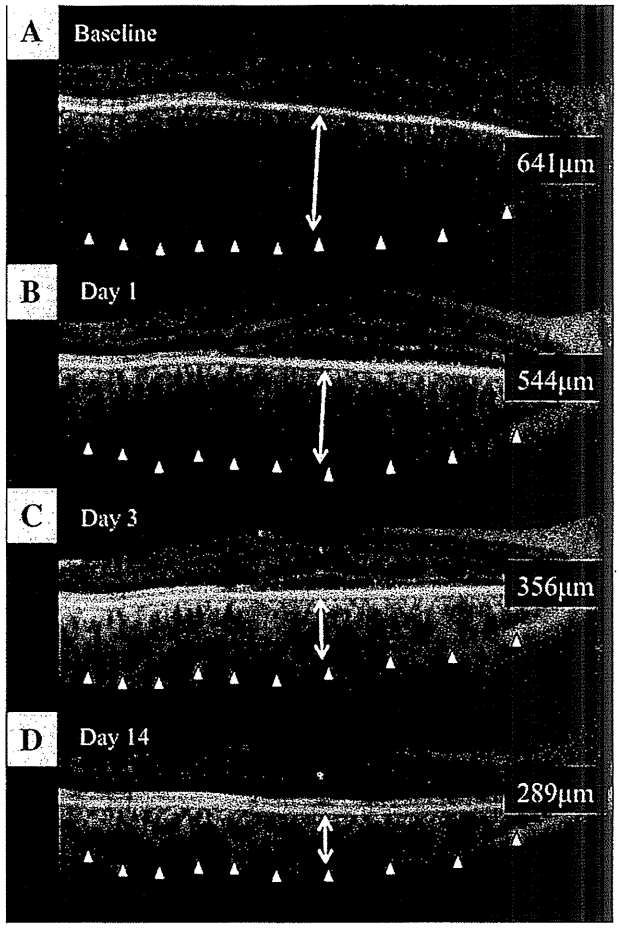

Fig. 3. Enhanced depth imaging spectral-domain OCT images of Patient 8. All images obtained using the technique described in this article are inverted. **A.** The choroidal thickness in the right eye under the fovea from the horizontal scan is 641 μm at baseline. The height of retinal detachment in the right eye under the fovea from the horizontal scan was 189 μm. The choroidal thickness in the right eye decreased to 544 μm at Day 1 **(B)**, 356 μm at Day 3 **(C)**, and 289 μm at Day 14 **(D)** after corticosteroid treatment. Resolution of the retinal detachment is observed at Day 14. The best-corrected visual acuity on Day 14 was 0.8 (20/25) (0.10 logMAR) in the right eye.

decreased after corticosteroid treatment. The serous retinal detachment decreased concurrently. By 1 month after initiation of corticosteroid treatment, the choroidal thickness was normal and the serous retinal detachment resolved.

Vogt–Koyanagi–Harada disease is a multisystem disorder that causes a bilateral granulomatous panuveitis. Affected patients have hyperemia of the optic nerve head and exudative retinal detachments.[1,2,12,13] Patchy filling delay with hypofluorescent spots and indistinct visualization of the choroidal vessels during indocyanine green angiography are hallmarks of the disease.[3–7] Improvement in the indocyanine green angiographic findings can be seen with treatment, although there are residual effects, such as patchy filling that remain. B-mode ultrasound imaging is also one of the methods for choroidal evaluation in VKH disease.[14,15] However, the low resolution of contact B-mode ultrasonography and the anatomic alterations induced by the disease make visualization of the boundaries between the retina, the choroid, and the sclera difficult to discern.

Vogt–Koyanagi–Harada disease is usually treated with high-dose corticosteroids initially followed by a tapering oral dose.[1] Aggressive early treatment may prevent progression to the chronic recurrent stage.[18] In addition, chronic anterior uveitis and persistent choroidal inflammation may lead to development of choroidal neovascularization.[19,20] Thus, the evaluation of the treatment response is important in the therapy of VKH disease. Enhanced depth imaging OCT offers a method to directly visualize the choroid. The boundaries between the retina and the RPE and in turn between the RPE and the choroid are readily visible. However, if there is thickening of the choroid so that it is >1,000 μm, visualization of the boundary between the choroid and the inner sclera may be difficult. The test still has diagnostic utility at this point because a choroidal thickness of 1,000 μm is much greater than normal.[17]

In the current study, the left eye of Patient 4 showed the leakage from the optic nerve head during fluorescein angiography without serous retinal detachment. Because patchy filling delay and indistinct choroidal vessels were observed during indocyanine green angiography, meningismus with cerebrospinal fluid pleocytosis and the tinnitus were found, and because the fellow eye had a typical serous retinal detachment, we had diagnosed the papillitis type of VKH disease as being present in the left eye of Patient 4. However, it is possible that this case was seen earlier in the progression of disease before the development of a frank detachment. This case had choroidal thickening and might represent the precursor state to serous retinal detachment. These findings suggest that EDI-OCT could be used to evaluate various stages of VKH during follow-up by examining regions of the eye not otherwise visualized, such as the choroid, which appears to be primarily affected in VKH in the first place. In addition, because the papillitis type of VKH disease is sometimes misdiagnosed as optic neuritis,[21] examination of the choroid using EDI-OCT might be useful in differential diagnosis.

This retrospective study had several weaknesses including a small sample size and short-term follow-up. This study would require a much larger number of patients than was examined in the present study because of known interactions between choroidal thickness and age and also refractive error. More patients and longer

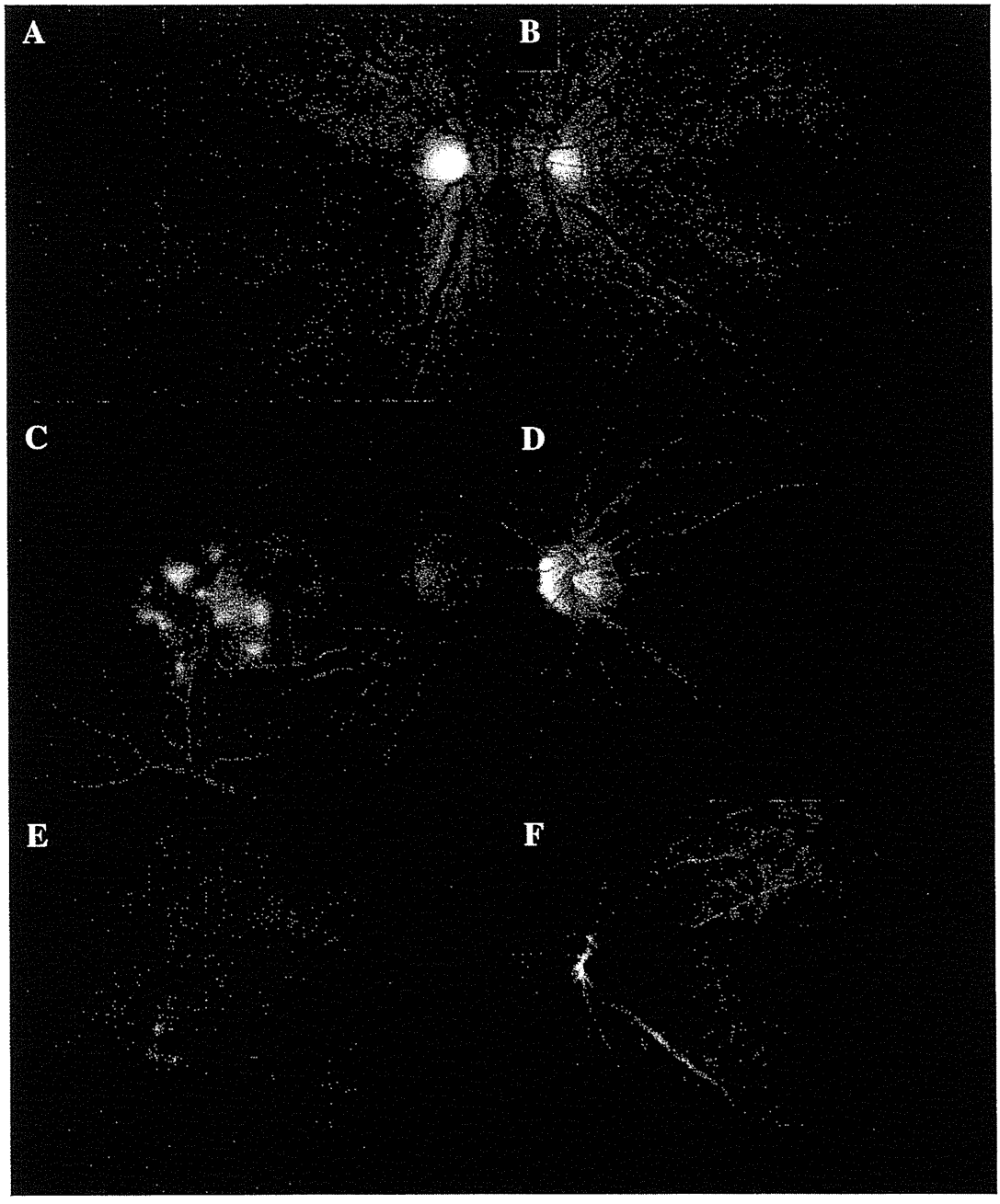

Fig. 4. Patient 4. A 17-year-old woman complained of decreased vision in the right eye for 2 days before presentation. The best-corrected visual acuity at baseline was 1.0 (20/20) (0.0 logMAR) in the right eye and 1.5 (20/13) (−0.18 logMAR) in the left eye. **A** and **B.** Monochromatic fundus photograph. At baseline, the right eye had a serous retinal detachment (**A**) and the left eye had foveal striate secondary to papillitis (**B**). **C** and **D.** Fluorescein angiography at baseline. **C.** Right eye showed multiple focal leaks and hyperfluorescence because of fluorescein pooling in the subretinal space. **D.** Left eye had fluorescein leakage from the optic disk. **E** and **F.** Indocyanine green angiography at baseline. Both eyes showed the multiple patchy filling delay with hypofluorescent spots and the indistinct choroidal vessels. She was diagnosed as having the ocular findings of VKH disease with serous retinal detachment in the right eye and papillitis in the left eye. She was given intravenous methylprednisolone (1000 mg, for 3 days) followed by tapered oral prednisolone starting at 40 mg/day.

follow-ups might provide the relationship among the choroidal thickness and the sign of the recurrence. In the current study, the acute stage of VKH disease showed marked choroidal thickening, which decreased dramatically after corticosteroid therapy. The serous retinal detachment concomitantly disappeared with the decrease in choroidal thickness. As opposed to central serous chorioretinopathy, which has a thickened choroid[18] and is adversely affected by corticosteroids, the excessive thickening in the choroid and the serous retinal

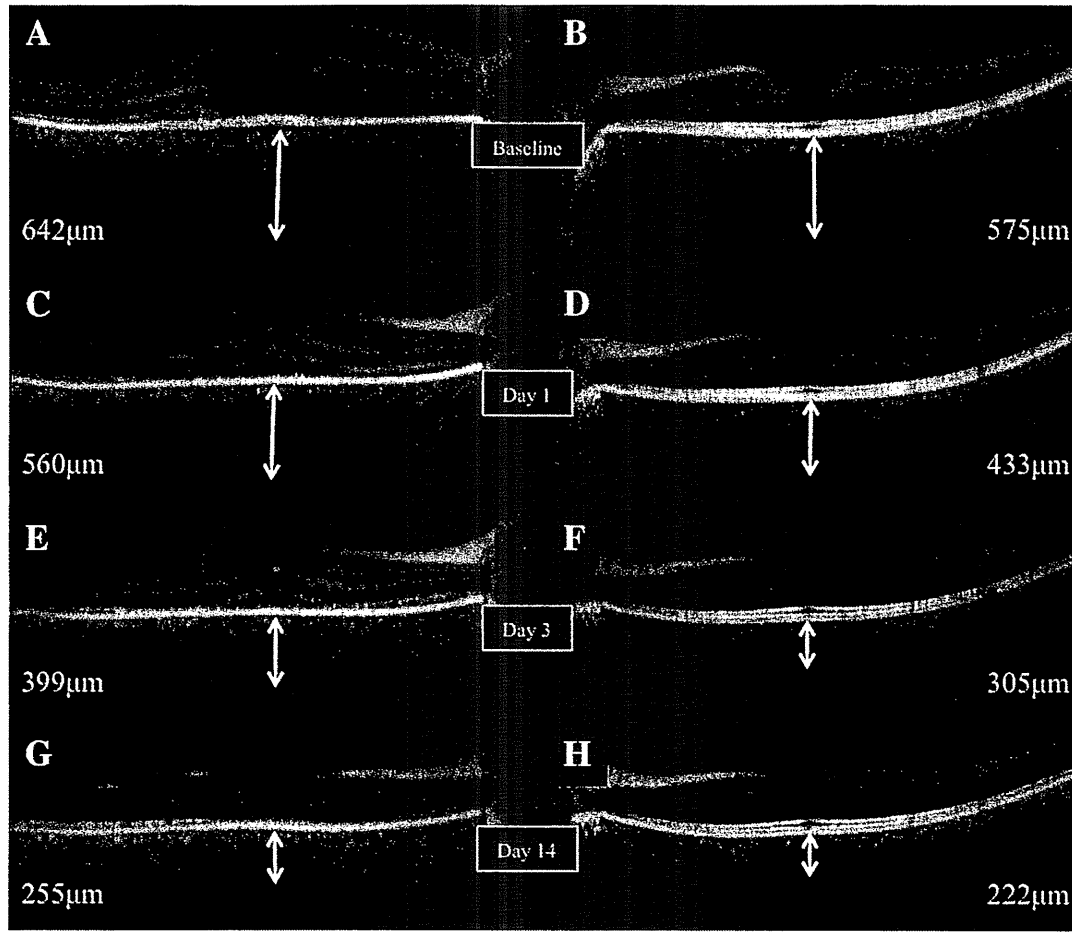

Fig. 5. Enhanced depth imaging spectral-domain OCT images of Patient 4. All images obtained using the technique described in this article were inverted. The right eye shows serous retinal detachment, and the left eye had no serous retinal detachment at baseline. The choroidal thickness from the horizontal scan was 642 μm in the right eye **(A)** and 575 μm in the left eye **(B)** at baseline, 560 μm in the right eye **(C)** and 433 μm in the left eye **(D)** at Day 1, 399 μm in the right eye **(E)** and 305 μm in the left eye **(F)** at Day 3, and 255 μm in the right eye **(G)** and 222 μm in the left eye **(H)** at Day 14. Resolution of the retinal detachment in the right eye was observed at Day 14. The best-corrected visual acuity on Day 14 was 1.2 (20/17) (−0.08 logMAR) in the right eye.

detachment in VKH are probably both primarily and secondarily related to inflammation, through increased vascular leakage. Enhanced depth imaging OCT is a very easy and useful adjunct to evaluate the choroidal involvement in VKH disease noninvasively.

Key words: Vogt–Koyanagi–Harada disease, enhanced depth imaging spectral-domain optical coherence tomography, choroidal thickness, retinal detachment, corticosteroid.

References

1. Moorthy RS, Inomata H, Rao NA. Vogt-Koyanagi-Harada syndrome. Surv Ophthalmol 1995;39:265–292.
2. Read RW, Holland GN, Rao NA, et al. Revised diagnostic criteria for Vogt-Koyanagi-Harada disease: report of an international committee on nomenclature. Am J Ophthalmol 2001;131:647–652.
3. Okada AA, Mizusawa T, Sakai J, Usui M. Videofunduscopy and videoangiography using the scanning laser ophthalmoscope in Vogt-Koyanagi-Harada syndrome. Br J Ophthalmol 1998;82:1175–1181.
4. Oshima Y, Harino S, Hara Y, Tano Y. Indocyanine green angiographic findings in Vogt-Koyanagi-Harada disease. Am J Ophthalmol 1996;122:58–66.
5. Kohno T, Miki T, Shiraki K, et al. Subtraction ICG angiography in Harada's disease. Br J Ophthalmol 1999;83:822–833.
6. Spaide RF, Goldbaum M, Wong DW, Tang KC, Iida T. Serous detachment of the retina. Retina 2003;23:820–846.
7. Herbort CP, Mantovani A, Bouchenaki N. Indocyanine green angiography in Vogt-Koyanagi-Harada disease: angiographic signs and utility in patient follow-up. Int Ophthalmol 2007;27:173–182.
8. Maruyama Y, Kishi S. Tomographic features of serous retinal detachment in Vogt-Koyanagi-Harada syndrome. Ophthalmic Surg Lasers Imaging 2004;35:239–242.
9. Tsujikawa A, Yamashiro K, Yamamoto K, Nonaka A, Fujihara M, Kurimoto Y. Retinal cystoid spaces in acute Vogt-Koyanagi-Harada syndrome. Am J Ophthalmol 2005;139:670–677.
10. Yamaguchi Y, Otani T, Kishi S. Tomographic features of serous retinal detachment with multilobular dye pooling in acute Vogt-Koyanagi-Harada disease. Am J Ophthalmol 2007;144:260–265.
11. Gupta V, Gupta A, Gupta P, Sharma A. Spectral-domain cirrus optical coherence tomography of choroidal striations seen in the acute stage of Vogt-Koyanagi-Harada disease. Am J Ophthalmol 2009;147:148.e2–153.e2.

12. Shimizu K. Harada's, Behcet's, Vogt-Koyanagi syndromes—are they clinical entities? Trans Am Acad Ophthalmol Otolaryngol 1973;77:OP281–OP290.
13. Ohno S, Char DH, Kimura SJ, O'Connor GR. Vogt-Koyanagi-Harada syndrome. Am J Ophthalmol 1977;83: 735–740.
14. Forster DJ, Cano MR, Green RL, Rao NA. Echographic features of the Vogt-Koyanagi-Harada syndrome. Arch Ophthalmol 1990;108:1421–1426.
15. Hewick SA, Fairhead AC, Culy JC, Atta HR. A comparison of 10 MHz and 20 MHz ultrasound probes in imaging the eye and orbit. Br J Ophthalmol 2004;88:551–555.
16. Spaide RF, Koizumi H, Pozonni MC. Enhanced depth imaging spectral-domain optical coherence tomography. Am J Ophthalmol 2008;146:496–500.
17. Margolis R, Spaide RF. A pilot study of enhanced depth imaging optical coherence tomography of the choroid in normal eyes. Am J Ophthalmol 2009;147:811–815.
18. Bykhovskaya I, Thorne JE, Kempen JH, Dunn JP, Jabs DA. Vogt-Koyanagi-Harada disease: clinical outcomes. Am J Ophthalmol 2005;140:674–678.
19. Moorthy RS, Chong LP, Smith RE, Rao NA. Subretinal neovascular membranes in Vogt-Koyanagi-Harada syndrome. Am J Ophthalmol 1993;116:164–170.
20. Read RW, Rechodouni A, Butani N, et al. Complications and prognostic factors in Vogt-Koyanagi-Harada disease. Am J Ophthalmol 2001;131:599–606.
21. Rajendram R, Evans M, Khurana RN, Tsai JH, Rao NA. Vogt–Koyanagi–Harada disease presenting as optic neuritis. Int Ophthalmol 2007;27:217–220.

Subfoveal Retinal and Choroidal Thickness After Verteporfin Photodynamic Therapy for Polypoidal Choroidal Vasculopathy

ICHIRO MARUKO, TOMOHIRO IIDA, YUKINORI SUGANO, MASAAKI SAITO, AND TETSUJU SEKIRYU

• PURPOSE: To evaluate the morphologic retinal and choroidal changes after verteporfin photodynamic therapy (PDT) with and without ranibizumab for polypoidal choroidal vasculopathy using spectral-domain optical coherence tomography.

• DESIGN: Retrospective, comparative series.

• METHODS: The enhanced depth imaging optical coherence tomography technique was used in this retrospective, comparative series to measure the subfoveal retinal and choroidal thicknesses before and after treatment.

• RESULTS: Twenty-seven eyes with polypoidal choroidal vasculopathy were examined retrospectively. Sixteen eyes were treated with PDT monotherapy (PDT group). Eleven eyes were treated with PDT after intravitreal ranibizumab injection (ranibizumab plus PDT group). The polypoidal lesions regressed in all cases at 3 months. The mean retinal thickness, including the retinal detachment, increased from 401 ± 157 μm before treatment to 506 ± 182 μm 2 days after PDT ($P < .001$) and decreased to 365 ± 116 μm by 1 week after treatment ($P = .03$) and 265 ± 127 μm by 6 months after treatment ($P < .001$). The mean choroidal thickness increased from 269 ± 107 μm before treatment to 336 ± 96 μm 2 days after PDT treatment ($P < .001$ compared with baseline) and decreased to 262 ± 96 μm by 1 week after treatment ($P = .24$) and 229 ± 104 μm by 6 months ($P < .001$). Although the choroidal thickness showed a similar trend with both therapies, the retinal thickness in the ranibizumab plus PDT group remained thinner than that in the PDT group until 6 months after treatment.

• CONCLUSIONS: PDT was associated with decreased retinal and choroidal thicknesses. Combination therapy reduced the transient exudation after PDT in some cases, and monthly intravitreal ranibizumab injections maintained retinal thinning and seemed to improve vision better than PDT monotherapy. (Am J Ophthalmol 2011;151:594–603. © 2011 by Elsevier Inc. All rights reserved.)

Accepted for publication Oct 20, 2010.

From the Department of Ophthalmology, Fukushima Medical University School of Medicine, Fukushima, Japan (I.M., T.I., Y.S., M.S., Y.S.).

Inquiries to Ichiro Maruko, Department of Ophthalmology, Fukushima Medical University School of Medicine, 1 Hikarigaoka, Fukushima, Japan; e-mail: imaruko@fmu.ac.jp

VERTEPORFIN PHOTODYNAMIC THERAPY ([PDT], Visudine; Novartis, Basel, Switzerland) is an established treatment for age-related macular degeneration (AMD)[1–5] and polypoidal choroidal vasculopathy (PCV).[5–11] However, complications after PDT have been reported,[12–24] such as transient subretinal or intraretinal fluid accumulation within 1 week after PDT and more severe and potential permanent vision loss secondary to subretinal bleeding. PDT using verteporfin for AMD also can cause choriocapillaris damage and vascular remodeling in the underlying choroid.[12–15,23,24]

Intravitreal ranibizumab (Lucentis; Genentech, South San Francisco, California, USA), an anti–vascular endothelial growth factor (VEGF) therapy, is the most commonly used therapy for AMD,[25–27] although the efficacy of anti-VEGF therapy for PCV may be less than that for typical choroidal neovascularization associated with AMD.[28–30] Since PDT is thought to induce VEGF expression,[19] combination therapy comprising PDT and pharmacologic agents[29,31–34] to inhibit VEGF expression also has been reported to increase the efficacy of both PDT and pharmacologic agents.

Spectral-domain optical coherence tomography (OCT) detects morphologic changes in the neurosensory retina in a variety of retinal and choroidal diseases. Recently, Spaide and associates reported a new method, enhanced depth imaging (EDI) OCT, to evaluate the choroidal status.[35]

In the current study, we retrospectively evaluated visual acuity (VA) changes and retinal and choroidal alterations after PDT for PCV using this noninvasive OCT technique. We also compared these changes after PDT with and without intravitreal injection of ranibizumab.

METHODS

THE CLINICAL EXAMINATIONS FOR DIAGNOSIS OF PCV INcluded indirect ophthalmoscopy, slit-lamp biomicroscopy with a contact lens or noncontact lens, digital fluorescein angiography, and indocyanine green angiography (ICGA). 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, Dos-

0002-9394/$36.00
doi:10.1016/j.ajo.2010.10.030

TABLE. The Clinical Changes of the Mean Choroidal Thickness and the Mean Retinal Thickness during the Follow-up Periods in the Photodynamic Therapy Alone Group and the Ranibizumab plus Photodynamic Therapy Group

Case No.	Gender	Age (yrs)	Eye	Treatment	BCVA at Baseline (logMAR)	BCVA at 6 Mos (logMAR)	Permeability[a]	Retinal Thickness (μm)[b]							Choroidal Thickness (μm)[c]						
								Baseline	Day 0	Day 2	1 Wk	1 Mo	3 Mos	6 Mos	Baseline	Day 0	Day 2	1 Wk	1 Mo	3 Mos	6 Mos
1	M	56	Left	PDT[d]	0.6 (0.22)	1.0 (0.00)	Yes	253		268	259	222	235	198	373		421	363	323	324	292
2	M	77	Left	PDT	0.1 (1.00)	0.3 (0.52)	Yes	345		512	394	293	293	209	337		414	295	215	204	208
3	M	58	Left	PDT	0.4 (0.40)	1.0 (0.00)	Yes	670		610	508	421	410	314	327		402	291	290	284	284
4	M	62	Left	PDT	0.6 (0.22)	0.8 (0.10)	Yes	374		465	373	211	190	191	191		251	174	134	129	129
5	M	86	Right	PDT	0.2 (0.70)	0.3 (0.52)	Yes	218		258	250	189	149	137	322		420	341	258	280	246
6	M	76	Left	PDT	0.5 (0.30)	0.5 (0.30)	Yes	230		297	267	230	279	201	307		352	320	306	282	278
7	M	69	Left	PDT	0.7 (0.15)	0.8 (0.10)	Yes	295		589	281	195	160	177	458		492	464	444	424	435
8	M	70	Left	PDT	0.6 (0.22)	0.9 (0.05)	Yes	281		438	343	227	216	208	348		364	335	312	307	323
9	F	76	Right	PDT	0.2 (0.70)	0.2 (0.70)	Yes	364		451	322	275	175	209	261		281	225	196	206	208
10	F	70	Left	PDT	0.4 (0.40)	0.7 (0.15)	Yes	385		436	345	328	321	307	290		306	286	264	243	265
11	M	82	Right	PDT	0.08 (1.10)	0.1 (1.00)	No	476		731	379	431	1037	681	250		266	228	216	191	146
12	M	82	Right	PDT	0.3 (0.52)	NA	No	435		548	408	178	168	NA	127		253	146	117	107	NA
13	M	86	Right	PDT	0.05 (1.30)	0.03 (1.52)	No	466		505	332	216	277	243	120		234	156	112	116	116
14	M	53	Left	PDT	0.3 (0.52)	0.4 (0.40)	No	276		345	234	232	270	326	159		268	177	158	168	178
15	F	68	Right	PDT	0.4 (0.40)	0.4 (0.40)	No	368		645	407	190	249	388	217		249	197	183	186	208
16	F	77	Right	PDT	0.4 (0.40)	1.2 (−0.08)	No	387		405	338	215	161	174	292		328	312	241	215	213
Mean ±		71.8			0.29 (0.53)	0.42 (0.37)		364		469	340	253	287	264	273		331	269	235	229	235
SD								114		137	72	78	212	134	93		80	88	88	85	83
17	M	55	Left	Ranibizumab + PDT[e]	0.5 (0.30)	0.8 (0.10)	Yes	348	313	305	257	190	179	276	604	595	645	510	508	505	508
18	M	78	Right	Ranibizumab + PDT	0.24 (0.62)	NA	Yes	542	535	951	516	406	330	NA	260	260	301	241	252	226	NA
19	F	67	Left	Ranibizumab + PDT	0.5 (0.30)	1.0 (0.00)	Yes	533	516	536	507	471	244	190	292	289	328	281	262	248	272
20	F	74	Left	Ranibizumab + PDT	0.5 (0.30)	0.8 (0.10)	Yes	213	207	544	186	128	150	174	344	351	425	371	311	323	383
21	F	72	Right	Ranibizumab + PDT	0.3 (0.52)	0.8 (0.10)	Yes	435	429	434	356	274	139	146	208	216	329	193	169	145	114
22	F	84	Right	Ranibizumab + PDT	0.01 (2.00)	0.04 (1.40)	Yes	955	853	1020	726	538	418	557	250	238	350	220	205	173	155
23	M	56	Right	Ranibizumab + PDT	0.3 (0.52)	0.4 (0.40)	No	324	328	312	246	221	213	228	248	248	273	229	198	224	245
24	M	67	Right	Ranibizumab + PDT	0.5 (0.30)	1.0 (0.00)	No	514	506	494	407	271	173	234	185	190	252	174	149	148	146
25	M	77	Left	Ranibizumab + PDT	0.3 (0.52)	0.8 (0.10)	No	476	464	506	394	230	181	188	224	229	401	273	205	164	176

Continued on next page

TABLE. Continued

Case No.	Gender	Age (yrs)	Eye	Treatment	BCVA at Baseline (logMAR)	BCVA at 6 Mos (logMAR)	Permeability[a]	Retinal Thickness (μm)[b]						Choroidal Thickness (μm)[c]					
								Baseline	Day 0	Day 2	1 Wk	1 Mo	3 Mos	6 Mos	Baseline	Day 0	Day 2	1 Wk	1 Mo	3 Mos	6 Mos
26	M	67	Left	Ranibizumab + PDT	0.4 (0.40)	0.3 (0.52)	No	400	404	610	520	380	319	320	111	109	212	114	95	98	91
27	F	84	Right	Ranibizumab + PDT	0.5 (0.30)	0.6 (0.22)	No	268	284	444	300	246	388	360	175	165	253	169	158	150	117
Mean ±		71.0			0.28 (0.55)	0.51 (0.29)		455	440	559	401	305	248	267	264	262	342	252	228	218	220
SD								198	173	230	157	127	99	122	129	127	119	109	110	113	134

BCVA = best-corrected visual acuity; F = female; logMAR = logarithm of the minimal angle of resolution; M = male; Mos = months; NA = not applicable; PDT = photodynamic therapy; SD = standard deviation; Wk = week; yrs = years.

[a]Choroidal vascular hyperpermeability.

[b]Choroidal thickness measured using the enhanced depth imaging spectral-domain optical coherence tomography technique.

[c]Retinal thickness including retinal detachment at the fovea.

[d]Photodynamic therapy with verteporfin. In the PDT alone group, measurement was at the fovea before PDT (baseline), 2 days after PDT (day 2), 1 week after PDT (1W), 1 month after laser PDT (1M), 3 months after PDT (3M), and 6 months after PDT (6M).

[e]Intravitreal ranibizumab injection plus PDT. In the ranibizumab plus PDT group, measurement was at the fovea before ranibizumab (baseline), before PDT (day 0), 2 days after PDT (day 2), 1 week after PDT (1W), 1 month after PDT (1M), 3 months after PDT (3M), and 6 months after PDT (6M).

senheim, Germany). The best-corrected visual acuity (BCVA) was measured with a Japanese standard decimal visual chart and converted to the logarithm of the minimal angle of resolution (logMAR) scale for analysis. All eyes were examined with the Heidelberg Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany).

In the current study, diagnostic criteria for PCV were proposed based on ICGA findings, which imaged the characteristic aneurysmal lesions. All patients with PCV had choroidal neovascularization on fluorescein angiography, which was identified as PCV on ICGA. Choroidal vascular hyperpermeability, seen as hyperfluorescence in middle-phase ICGA images, also was evaluated.

Consecutive patients with PCV were treated with PDT monotherapy (PDT group) between January 2009 and May 2009 and were treated with the combination therapy of intravitreal ranibizumab and PDT (ranibizumab plus PDT group) between June 2009 and October 2009. Ranibizumab became available for medical use in Japan in March 2009.

The patients in the ranibizumab plus PDT group were treated 1 or 2 days before PDT with intravitreal ranibizumab (0.5 mg/0.05 mL) injected 3.5 to 4.0 mm posterior to the corneal limbus into the vitreous cavity using a 30-gauge needle after topical anesthesia was applied. Consecutive monthly intravitreal ranibizumab injections were administered for 3 months.

PDT was performed in both groups using the standard dose (6 mg/m^2) of verteporfin according to the protocol of the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy studies,[1,2] except for the greatest linear dimension (GLD). The GLD and treatment spot size were measured on ICGA (ICG-guided PDT) to reduce the exposed area.[36–38] The diameter of the PDT treatment spot size was the GLD plus 1 mm. A 689-nm laser system (Carl Zeiss, Dublin, California, USA) was used, and 50 J/cm^2 of energy was delivered with an 83-second exposure time. Angiographic evaluation in all cases was examined at 3 months after PDT, and additional treatment was performed if needed.

The retinal thickness, defined as the distance between the inner surface of the neurosensory retina and the inner surface of the retinal pigment epithelium, including retinal detachments at the fovea, also was measured at the same time. Spaide and associates reported observing the morphologic choroidal changes using the EDI OCT technique, which obtained inverted and highlighted choroidal images by moving the OCT device close to the eye.[35] All images were obtained using an eye-tracking system, and 100 scans were averaged automatically to improve the signal-to-noise ratio. We measured the choroidal thickness, defined as the zonal area between the outer surface of the retinal pigment epithelium and the inner scleral surface, from vertical and horizontal sections under the center of the fovea from OCT data, and these were averaged.

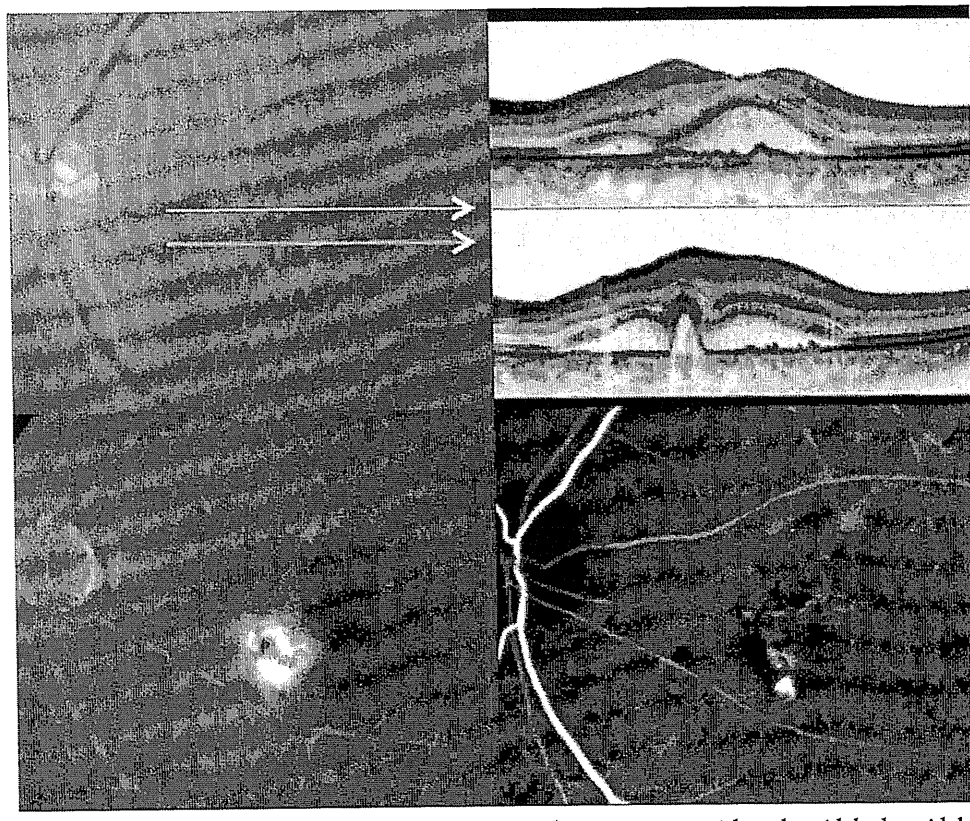

FIGURE 1. Case 4, a representative case from the photodynamic therapy group with polypoidal choroidal vasculopathy, is a 62-year-old man who sought treatment for decreased vision in the left eye 2 weeks previously. (Top left) Gray-scale fundus photograph of the left eye showing a serous retinal detachment at the center of the macular area and an elevated orange-red lesion at the lower area nasal to the fovea. The white horizontal arrows indicate the line through the fovea and orange-red lesions, respectively. (Top right) Spectral-domain optical coherence tomography images of the left eye showing the serous retinal detachment, retinal pigment epithelium irregularity, and a sharp protrusion. The upper and lower images correspond to the arrows on the gray-scale fundus photography, respectively. (Bottom left) Middle-phase fluorescein angiography image showing leakage in the lower area nasal to the fovea. (Bottom right) Middle-phase indocyanine green angiography image showing the polypoidal lesion and the abnormal vascular network at the macular area.

In the PDT group, the retinal and choroidal thicknesses at the center of the fovea were measured using the EDI OCT before PDT (baseline) and after PDT at 2 days, 1 week, and 1, 3, and 6 months. In the ranibizumab plus PDT group, the retinal and choroidal thicknesses at the center of the fovea also were measured by EDI OCT before intravitreal injection of ranibizumab (baseline), before PDT on day 1 or 2 after the intravitreal ranibizumab injection (day 0), and after PDT at 2 days, 1 week, and 1, 3, and 6 months. OCT was performed at all visits. The patients who received their first PDT treatments remained in the hospital for 2 days to avoid sun exposure.

The reported measurements obtained from the OCT images represented the average of all the measurements. The coauthors (I.M., Y.S., M.S.) were masked to the treatment status. The VAs are expressed as decimal equivalents and logMAR equivalents. The BCVA and the measurement of the choroidal and retinal thickness were analyzed using the Wilcoxon signed-rank test (SPSS software version 17.0; SPSS, Inc, Chicago, Illinois, USA), and $P = .05$ or less was considered significant.

RESULTS

TWENTY-SEVEN EYES OF 27 CONSECUTIVE PATIENTS WITH newly diagnosed PCV were included. Sixteen eyes of 16 patients (12 men, 4 women; mean age, 71.8 years) comprised the PDT group. Eleven eyes of 11 patients (6 men, 5 women; mean age, 71.0 years) comprised the ranibizumab plus PDT group. The lesion area included the fovea in all cases. The mean GLD for PDT was 3013 ± 1059 μm in the PDT group and 2905 ± 1122 μm in the ranibizumab plus PDT group. ICGA showed that the polypoidal lesions in all cases in both groups regressed at 3 months. One eye in the ranibizumab plus PDT group needed retreatment; 3 eyes in the PDT group needed retreatment for the exuda-

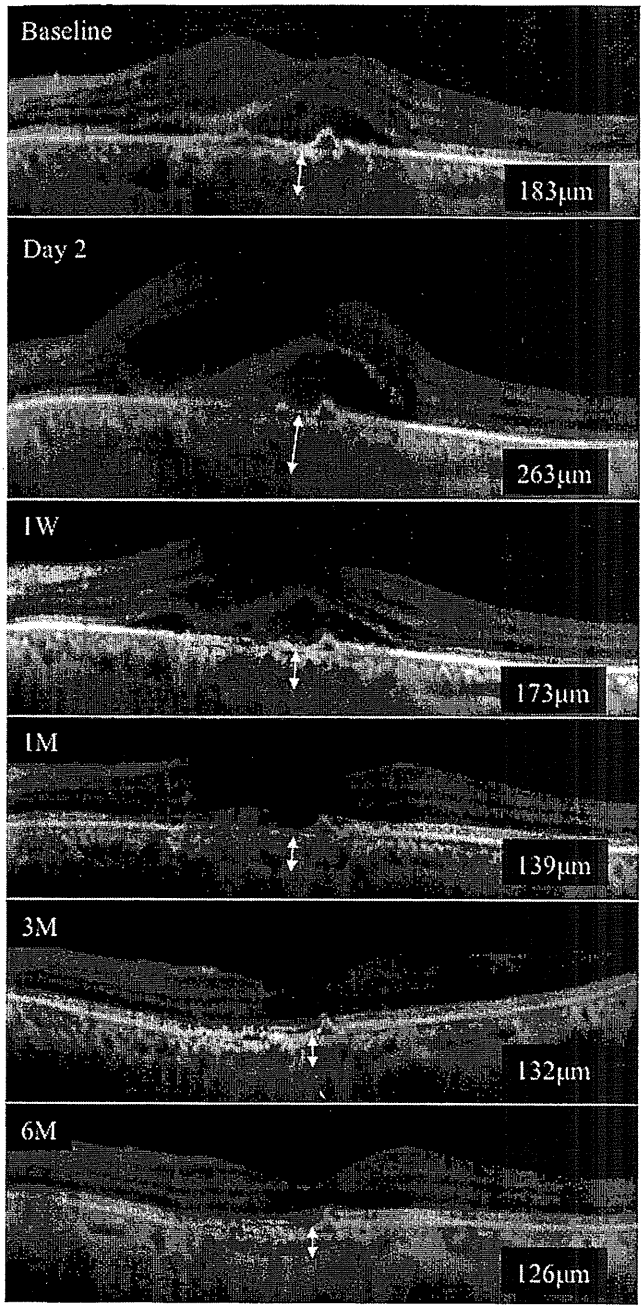

FIGURE 2. Enhanced depth imaging spectral-domain optical coherence tomography images of the same polypoidal choroidal vasculopathy case as in Figure 1. The choroidal thickness in the horizontal images at baseline (Top) was 183 μm, (Second row) increased markedly to 263 μm on day 2, (Third row) decreased to 173 μm at 1 week, (Fourth row) decreased to 139 μm at 1 month, (Fifth row) decreased to 132 μm at 3 months, and (bottom) decreased to 126 μm at 6 months. The serous retinal detachment resolved in 3 months. Baseline = before photodynamic therapy (PDT); day 2 = 2 days after PDT; 1 W = 1 week after PDT; 1 M = 1 month after PDT; 3 M = 3 months after PDT; 6 M = 6 months after PDT.

tive findings during the follow-up period. One patient in each group did not return for the 6-month visit.

The mean retinal thickness increased significantly ($P < .001$) from 401 ± 157 μm at baseline to 506 ± 182 μm on day 2 after PDT and decreased to 365 ± 116 μm by 1 week ($P = .03$), 274 ± 102 μm by 1 month ($P < .001$), 271 ± 174 μm by 3 months ($P < .001$), and 265 ± 127 μm by 6 months ($P < .001$). The mean choroidal thickness increased from 269 ± 107 μm at baseline to 336 ± 96 μm on day 2 after PDT ($P < .001$) and decreased to 262 ± 96 μm by 1 week ($P = .24$), 232 ± 96 μm by 1 month ($P < .001$), 225 ± 95 μm by 3 months ($P < .001$), and 229 ± 104 μm by 6 months ($P < .001$). The mean choroidal thickness of 16 eyes with choroidal vascular hyperpermeability in middle-phase baseline ICGA images was thicker than in 11 eyes without hyperpermeability (323 ± 99 μm vs 191 ± 60 μm; $P < .001$, Mann–Whitney U test).

The mean subfoveal retinal and choroidal thicknesses at baseline and the changes during follow-up in both groups are summarized in the Table. Figures 1 and 2 show representative cases in the PDT group. Figures 3 and 4 show representative cases in the ranibizumab plus PDT group.

In the PDT group, the mean choroidal thickness increased from 273 ± 93 μm at baseline to 331 ± 80 μm on day 2 ($P < .001$) and decreased to 269 ± 88 μm by 1 week ($P = .5$), 229 ± 85 μm by 3 months ($P < .001$), and 235 ± 83 μm by 6 months ($P < .001$). In the ranibizumab plus PDT group, the mean choroidal thickness increased from 264 ± 129 μm at baseline to 342 ± 119 μm on day 2 after PDT ($P = .003$) and decreased to 252 ± 109 μm by 1 week ($P = .21$), 218 ± 113 μm by 3 months ($P = .003$), and 220 ± 134 μm by 6 months ($P = .001$). The changes in the choroidal thicknesses in both groups were similar. The changes in the mean retinal thickness also showed a similar trend toward decreased thickness over 6 months. Although the mean retinal thickness in the PDT group increased significantly from 364 ± 114 μm at baseline to 469 ± 137 μm on day 2 after PDT ($P = .003$), that in the ranibizumab plus PDT group did not increase significantly on day 2 after PDT (455 ± 198 μm at baseline, 559 ± 230 μm on day 2; $P = .09$). Only 1 eye in the PDT group had retinal thinning on day 2 after PDT; however, 5 eyes in the ranibizumab plus PDT group had retinal thinning.

The changing ratios of the retinal and choroidal thicknesses compared with baseline in both groups are shown in Figure 5. Both graphs showed a similar curve after PDT; however, the percentage change of the retinal thickness at 6 months was 73% in the PDT group and 59% in the ranibizumab plus PDT group. The retinal thickness at 6 months remained relatively lower in the ranibizumab plus PDT group than in the PDT group.

The mean BCVA levels in all cases at baseline and at 1, 3, and 6 months were 0.29 (0.54 logMAR), 0.37 (0.43 logMAR), 0.42 (0.38 logMAR), and 0.46 (0.34 logMAR),

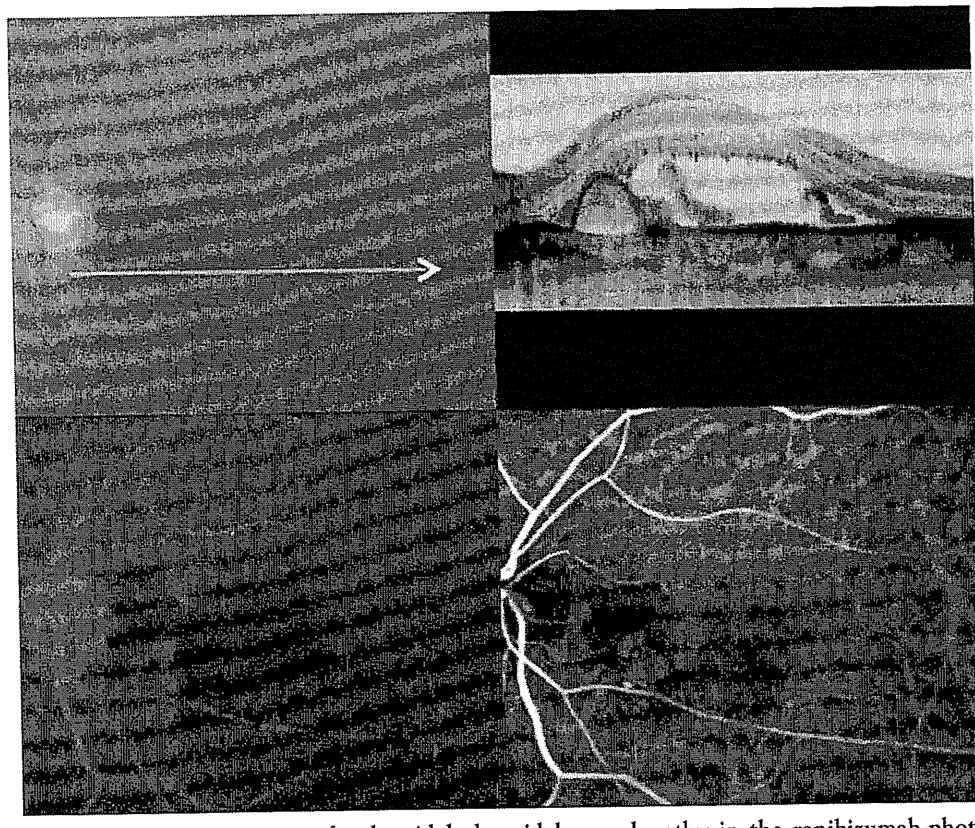

FIGURE 3. Case 25, a representative case of polypoidal choroidal vasculopathy in the ranibizumab-photodynamic therapy group, is a 77-year-old man who noted blurred vision in the left eye 2 weeks previously. (Top left) Gray-scale fundus photograph of the left eye showing a serous retinal detachment at the macular area and a subretinal hemorrhage between the optic disc and fovea. The white horizontal arrows indicate the line through the fovea. (Top right) Spectral-domain optical coherence tomography image of the left eye showing the serous retinal detachment at the macular area and a sharp protrusion temporal to the optic disc. The image corresponds to the arrows of the gray-scale fundus photograph. (Bottom left) Middle-phase fluorescein angiography image showing slight leakage at the lower area nasal to the fovea. (Bottom right) Middle-phase indocyanine green angiography image showing a polypoidal lesion and the abnormal vascular network at the lower-nasal area to the fovea.

respectively. There was a significant ($P < .001$) improvement from baseline to 6 months. The mean BCVA levels in the PDT group at the same time points were 0.29 (0.53 logMAR), 0.37 (0.43 logMAR), 0.37 (0.43 logMAR), and 0.42 (0.37 logMAR), respectively. The mean BCVA levels in the ranibizumab plus PDT group at the same time points were 0.28 (0.55 logMAR), 0.38 (0.42 logMAR), 0.49 (0.31 logMAR), and 0.51 (0.29 logMAR), respectively. Although both groups had significant improvements in VA compared with baseline ($P = .01$ in both groups), the BCVA in the ranibizumab plus PDT group was better than that in the PDT group (Figure 6).

DISCUSSION

IN THE CURRENT STUDY, PDT OCCLUDED THE POLYPOIDAL lesions and decreased the retinal and choroidal thicknesses in eyes with PCV. The combination therapy of ranibizumab and PDT reduced the exudation just after PDT and maintained the retinal thinning until 6 months after treatment. Consequently, the BCVA after combination therapy was relatively better than that after PDT monotherapy.

PCV is more common in Asia than in white persons[39,40] and is thought to account for approximately half of patients with neovascular AMD in Japan.[41] PDT for PCV is still an effective treatment in Japan because PDT may result in regression of polypoidal lesions.[5,9–11] Currently, intravitreal ranibizumab is the most common treatment for AMD worldwide because of the expect increase in BCVA.[24–26] However, there are increasing medical care costs and more regular hospital visits because of the need for monthly injections.[42,43] In addition, intravitreal ranibizumab for PCV is less effective than for AMD.[28–30]

Although transient exudation was seen within 1 week after PDT in the current study, the subfoveal choroidal thickness after PDT in both groups decreased at 6 months. ICGA in eyes with PCV sometimes shows choroidal vascular hyperpermeability,[44] which was observed in 16

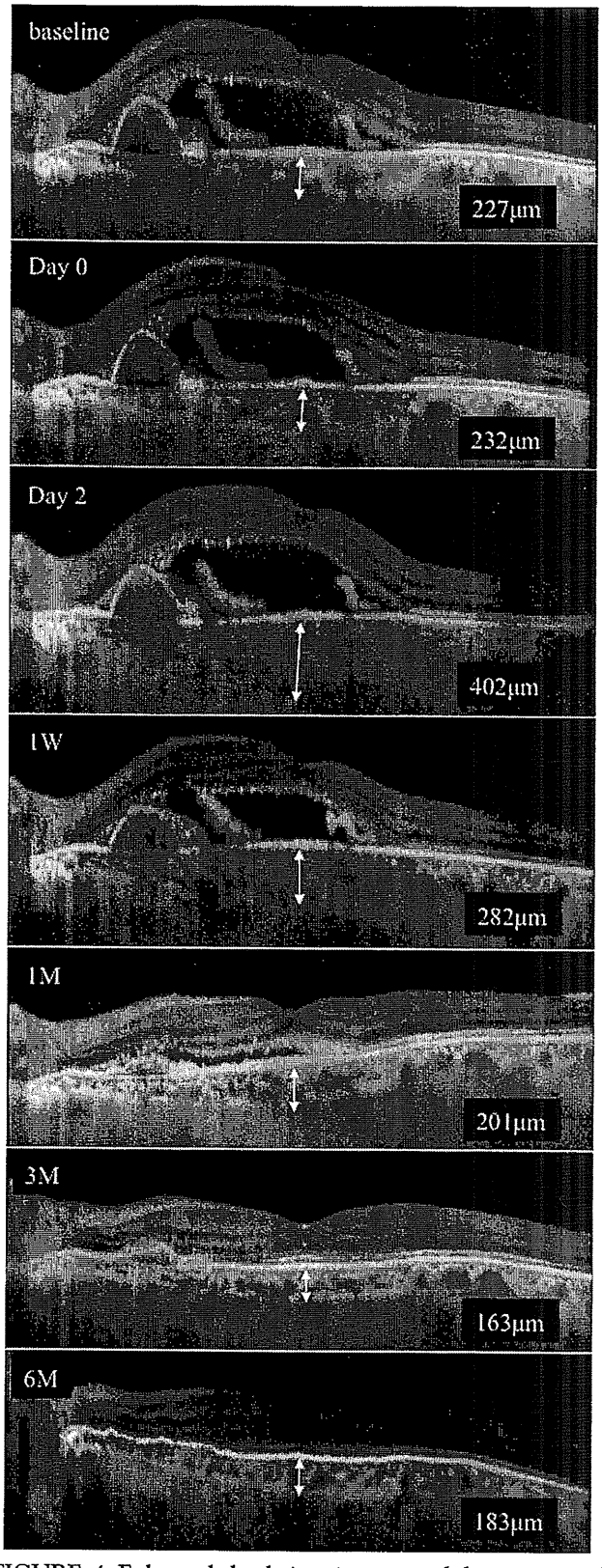

FIGURE 4. Enhanced depth imaging spectral-domain optical coherence tomography images in the same case of polypoidal choroidal vasculopathy as in Figure 3. The choroidal thicknesses in the horizontal images (Top) were 227 μm at baseline, (Second row) were 232 μm on day 0, (Third row) increased markedly to 402 μm on day 2, (Fourth row) decreased to 282 μm at 1 week, (Fifth row) decreased to 201 μm at 1 month, (Sixth row) decreased to 163 μm at 3 months, and (Bottom) increased to 183 μm at 6 months after treatment. The serous retinal detachment resolved at 3 months. Baseline = before intravitreal ranibizumab; day 0 = before photodynamic therapy (PDT); day 2 = 2 days after PDT; 1 W = 1 week after PDT; 1 M = 1 month after PDT; 3 M = 3 months after PDT; 6 M = 6 months after PDT.

eyes in the current study. In patients with central serous chorioretinopathy (CSC), the choroid is thicker because of choroidal vascular hyperpermeability.[45] Serous retinal detachments develop more often than in typical AMD,[46] which may indicate that some cases of PCV are similar to central serous chorioretinopathy with a thickened choroid. In the current study, the choroid in eyes with choroidal vascular hyperpermeability was thicker than in eyes without hyperpermeability. All 10 eyes with hyperpermeability had retinal thinning at 6 months; however, 3 of 6 eyes without hyperpermeability had increased retinal thickness at 6 months in the PDT group. These findings may indicate that the activity of PCV could be evaluated by choroidal hyperpermeability. We previously reported that half-dose PDT in patients with chronic central serous chorioretinopathy reduced the choroidal thickness and caused serous retinal detachments to regress on EDI OCT.[47] These findings may suggest that the efficacy of PDT for PCV is associated with not only regression of polypoidal lesions, but also with reduced choroidal vascular hyperpermeability.

Combination therapy has been expected to require frequent intravitreal injections to enhance treatment efficacy.[29,31–34] Some studies have reported that pharmacology-assisted PDT can reduce choriocapillaris occlusion.[24,33]

In the current study, although the same trends in choroidal thickness in both treatment groups were observed after treatment, combination therapy compared with PDT monotherapy inhibited the temporary increase in retinal thickness in some cases and maintained the retinal thinning until 6 months of follow-up. Inhibition of the transient reaction after PDT in the ranibizumab plus PDT group was expected because of the transient induction of VEGF expression.[19] Combination therapy significantly reduced the temporary exudation just after PDT; however, transient retinal thickening occurred in some cases. It is possible to inhibit the temporary inflammation using, for example, a steroid. Even with uncontrolled transient exudation after PDT, 3 consecutive monthly intravitreal ranibizumab injections may maintain the retinal thinning at 6 months and may help improve the VA. One patient had a recurrence after combination therapy, whereas 3 cases had a recurrence after PDT monotherapy during the follow-up period, which may indicate that ranibizumab also prevents fluid

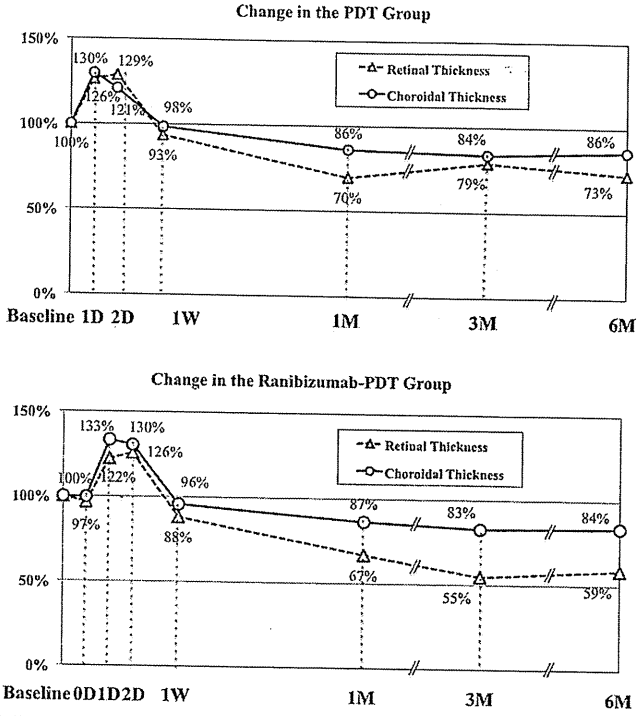

FIGURE 5. Graphs showing the percentage changes in the retinal and choroidal thicknesses during the follow-up period. (Top) Graph showing the percentage changes in the retinal and choroidal thicknesses after photodynamic therapy (PDT) compared with baseline. The open triangles with the connecting dashed line indicate the retinal thickness; the open circles with the connecting solid line indicate the changes in the choroidal thickness. Both the retinal and choroidal thicknesses increased at 1 and 2 days after treatment and decreased at 1 week and 1 month. The retinal thickness at 3 and 6 months increased slightly from that at 1 month. Baseline = before photodynamic therapy (PDT); 1 D = 1 day after PDT; 2 D = 2 days after PDT; 1 W = 1 week after PDT; 1 M = 1 month after PDT; 3 M = 3 months after PDT; 6 M = 6 months after PDT. (Bottom) Graph showing changes in the ranibizumab plus PDT group. Percentage changes in the retinal and choroidal thickness after intravitreal ranibizumab injections and PDT are compared with baseline. The open triangles with the connecting dashed line indicate the retinal thickness; the open circles with the connecting solid line indicate the changes in the choroidal thickness. Both the retinal and choroidal thicknesses were the same at 0 day, increased at 1 and 2 days, and decreased at 1, 3, and 6 months. The choroidal thickness at 1 week returned to baseline, and the retinal thickness at 1 week already decreased below baseline. The retinal thickness at 6 months remained lower than at baseline. Baseline = before intravitreal ranibizumab injection; 0 D = before PDT; 1 D = 1 day after PDT; 2 D = 2 days after PDT; 1 W = 1 week after PDT; 1 M = 1 month after PDT; 3 M = 3 months after PDT; 6 M = 6 months after PDT.

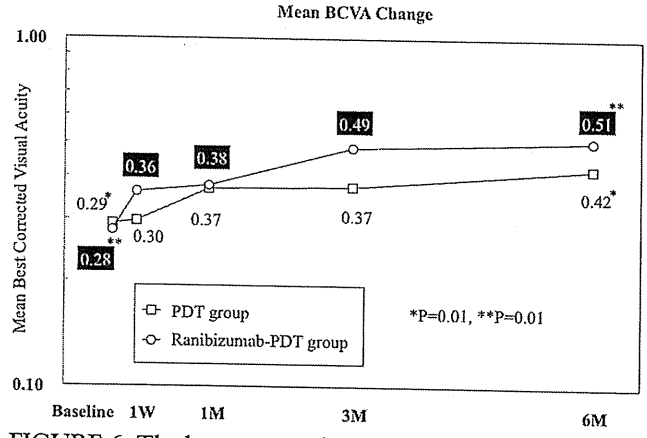

FIGURE 6. The best-corrected visual acuity (BCVA) changes in the photodynamic therapy (PDT) group and the ranibizumab plus PDT group. The open circles indicate the ranibizumab plus PDT group; the open squares indicate the PDT group. The mean BCVA between baseline and 6 months improved significantly more in the ranibizumab plus PDT group ($P = .01$) than in the PDT group ($P = .01$). Baseline = before intravitreal ranibizumab injection in the ranibizumab PDT group and before PDT in the PDT group; 1 W = 1 week after PDT; 1 M = 1 month after PDT; 3 M = 3 months after PDT; 6 M = 6 months after PDT.

from permeating the retinal pigment epithelium from the choroid intraretinally or subretinally. Although a study with more patients and longer follow-up is needed, combination therapy may help to resolve the medical and economic problems.

This retrospective study had several weaknesses. It was a pilot study with few patients and a short-term follow-up period for a new technique. Another study should evaluate the interactions between the choroidal thickness and age and refractive error. However, we believe the current findings suggest the importance of measuring the choroidal thickness during follow-up and understanding the treatment effectiveness.

In conclusion, both PDT monotherapy and combination therapy caused regression of the polypoidal lesions and decreased the retinal and choroidal thicknesses because of reduced choroidal vascular hyperpermeability. Combination therapy could reduce the transient exudation immediately after PDT, could maintain the retinal thinning with monthly intravitreal ranibizumab injections, and could improve the vision better than PDT monotherapy. EDI OCT noninvasively monitored the proposed site for the pathophysiologic changes in the retina and choroid and provided information not available by other means.

THE AUTHORS INDICATE NO FINANCIAL SUPPORT OR FINANCIAL CONFLICT OF INTEREST. INVOLVED IN DESIGN AND conduct of study (I.M., T.I., M.S.); Collection of data (I.M., Y.S.); Management, analysis, and interpretation of data (I.M., T.I., T.S.); Preparation and review of manuscript (I.M., T.I.); and Approval of the manuscript (I.M., T.I., Y.S., M.S., T.S.). This study followed the tenets of the Declaration of Helsinki. The Institutional Review Board at Fukushima Medical University School of Medicine approved optical coherence tomography observation for

eyes with macular and retinal disorders, the observational study for age-related macular degeneration and its similar disorders at the treatment and follow-up, and the retrospective comparative analysis performed in this study.

REFERENCES

1. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials—TAP Report 1. Arch Ophthalmol 1999;117(10):1329–1345.
2. Japanese Age-Related Macular Degeneration Trial (JAT) Study Group. Japanese age-related macular degeneration trial: 1-year results of photodynamic therapy with verteporfin in Japanese patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration. Am J Ophthalmol 2003;136(6):1049–1061.
3. Verteporfin Roundtable 2000 and 2001 Participants; Study Group Principal Investigators. Guidelines for using verteporfin (Visudyne) in photodynamic therapy to treat choroidal neovascularization due to age-related macular degeneration and other causes. Retina 2002;22(1):6–18.
4. Verteporfin Roundtable Participants. Guidelines for using verteporfin (Visudyne) in photodynamic therapy for choroidal neovascularization due to age-related macular degeneration and other causes: update. Retina 2005;25(2):119–134.
5. Tano Y, Ophthalmic PDT Study Group. Guidelines for PDT in Japan. Ophthalmology 2008;115(3):585–585.e6.
6. Quaranta M, Mauget-Faŝse M, Coscas G. Exudative idiopathic polypoidal choroidal vasculopathy and photodynamic therapy with verteporfin. Am J Ophthalmol 2002;134(2):277–280.
7. Spaide RF, Donsoff I, Lam DL, et al. Treatment of polypoidal choroidal vasculopathy with photodynamic therapy. Retina 2002;22(5):529–535.
8. Chan WM, Lam DS, Lai TY, et al. Photodynamic therapy with verteporfin for symptomatic polypoidal choroidal vasculopathy: one-year results of a prospective case series. Ophthalmology 2004;111(8):1576–1584.
9. Otani A, Sasahara M, Yodoi Y, et al. Indocyanine green angiography: guided photodynamic therapy for polypoidal choroidal vasculopathy. Am J Ophthalmol 2007;144(1):7–14.
10. Akaza E, Mori R, Yuzawa M. Long-term results of photodynamic therapy of polypoidal choroidal vasculopathy. Retina 2008;28(5):717–722.
11. Saito M, Iida T, Nagayama D. Photodynamic therapy with verteporfin for age-related macular degeneration or polypoidal choroidal vasculopathy: comparison of the presence of serous retinal pigment epithelial detachment. Br J Ophthalmol 2008;92(12):1642–1647.
12. Schmidt-Erfurth U, Hasan T, Gragoudas E, et al. Vascular targeting in photodynamic occlusion of subretinal vessels. Ophthalmology 1994;101(12):1953–1961.
13. Kramer M, Miller JW, Michaud N, et al. Liposomal benzoporphyrin derivative verteporfin photodynamic therapy. Selective treatment of choroidal neovascularization in monkeys. Ophthalmology 1996;103(3):427–438.
14. Schmidt-Erfurth U, Laqua H, Schlötzer-Schrehard U, et al. Histopathological changes following photodynamic therapy in human eyes. Arch Ophthalmol 2002;120(6):835–844.
15. Schlötzer-Schrehardt U, Viestenz A, Naumann GO, et al. Dose-related structural effects of photodynamic therapy on choroidal and retinal structures of human eyes. Graefes Arch Clin Exp Ophthalmol 2002;240(9):748–757.
16. Schmidt-Erfurth U, Michels S, Barbazetto I, Laqua H. Photodynamic effects on choroidal neovascularization and physiological choroid. Invest Ophthalmol Vis Sci 2002;43(3):830–841.
17. Rogers AH, Martidis A, Greenberg PB, Puliafito CA. Optical coherence tomography findings following photodynamic therapy of choroidal neovascularization. Am J Ophthalmol 2002;134(4):566–576.
18. Costa RA, Farah ME, Cardillo JA, et al. Immediate indocyanine green angiography and optical coherence tomography evaluation after photodynamic therapy for subfoveal choroidal neovascularization. Retina 2003;23(2):159–165.
19. Schmidt-Erfurth U, Schlötzer-Schrehard U, Cursiefen C, et al. Influence of photodynamic therapy on expression of vascular endothelial growth factor (VEGF), VEGF receptor 3, and pigment epithelium-derived factor. Invest Ophthalmol Vis Sci 2003;44(10):4473–4480.
20. Hirami Y, Tsujikawa A, Otani A, et al. Hemorrhagic complications after photodynamic therapy for polypoidal choroidal vasculopathy. Retina 2007;27(3):335–341.
21. Ishikawa K, Kondo M, Ito Y, et al. Correlation between focal macular electroretinograms and angiographic findings after photodynamic therapy. Invest Ophthalmol Vis Sci 2007;48(5):2254–2259.
22. Koizumi H, Iida T, Nagayama D, et al. Indocyanine green angiography in eyes with substantially increased subretinal fluid 1 week after photodynamic therapy. Retinal Cases & Brief reports 2008;2(1):12–14.
23. Isola V, Pece A, Parodi MB. Choroidal ischemia after photodynamic therapy with verteporfin for choroidal neovascularization. Am J Ophthalmol 2006;142(4):885–887.
24. Mukai R, Kishi S, Sato T, et al. Protective effect of intravitreal bevacizumab and sub-tenon triamcinolone acetonide against occlusion of choriocapillaris induced by photodynamic therapy. Ophthalmologica 2010;224(5):267–273.
25. Boyer DS, Antoszyk AN, Awh CC, et al, MARINA Study Group. Subgroup analysis of the MARINA study of ranibizumab in neovascular age-related macular degeneration. Ophthalmology 2007;114(2):246–252.
26. Kaiser PK, Brown DM, Zhang K, et al. Ranibizumab for predominantly classic neovascular age-related macular degeneration: subgroup analysis of first-year ANCHOR results. Am J Ophthalmol 2007;144(6):850–857.
27. Kaiser PK, Blodi BA, Shapiro H, Acharya NR, MARINA Study Group. Angiographic and optical coherence tomographic results of the MARINA study of ranibizumab in neovascular age-related macular degeneration. Ophthalmology 2007;114(10):1868–1875.

28. Gomi F, Sawa M, Sakaguchi H, et al. Efficacy of intravitreal bevacizumab for polypoidal choroidal vasculopathy. Br J Ophthalmol 2008;92(1):70–73.
29. Lai TY, Chan WM, Liu DT, et al. Intravitreal bevacizumab (Avastin) with or without photodynamic therapy for the treatment of polypoidal choroidal vasculopathy. Br J Ophthalmol 2008;92(5):661–666.
30. Kokame GT, Yeung L, Lai JC. Continuous anti-VEGF treatment with ranibizumab for polypoidal choroidal vasculopathy: an Interim 6-month report. Br J Ophthalmol 2010; 94(3):297–301.
31. Antoszyk AN, Tuomi L, Chung CY, Singh A, FOCUS Study Group. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration (FOCUS): year 2 results. Am J Ophthalmol 2008; 145(5):862–874.
32. Saito M, Shiragami C, Shiraga F, et al. Combined intravitreal bevacizumab and photodynamic therapy for retinal angiomatous proliferation. Am J Ophthalmol 2008;146(6): 935–941.e1.
33. Kiss CG, Simader C, Michels S, Schmidt-Erfurth U. Combination of verteporfin photodynamic therapy and ranibizumab: effects on retinal anatomy, choroidal perfusion and visual function in the protect study. Br J Ophthalmol 2008;92(12):1620–1627.
34. Kaiser PK; Registry of Visudyne AMD Therapy Writing Committee. Verteporfin photodynamic therapy combined with intravitreal bevacizumab for neovascular age-related macular degeneration. Ophthalmology 2009;116(4):747–755, 755.e1.
35. Spaide RF, Koizumi H, Pozonni MC. Enhanced depth imaging spectral-domain optical coherence tomography. Am J Ophthalmol 2008;146(4):496–500.
36. Wygnanski-Jaffe T, Desatnik H, Alhalel A, et al. ICG angiography-guided photodynamic therapy for large pigment epithelial detachments in age-related macular degeneration. Ophthalmic Surg Lasers Imaging 2006;37(5):358–363.
37. Otani A, Sasahara M, Yodoi Y, et al. Indocyanine green angiography: guided photodynamic therapy for polypoidal choroidal vasculopathy. Am J Ophthalmol 2007;144(1): 7–14.
38. Eandi CM, Ober MD, Freund KB, et al. Selective photodynamic therapy for neovascular age-related macular degeneration with polypoidal choroidal neovascularization. Retina 2007;27(7):825–831.
39. Yannuzzi LA, Wong DW, Sforzolini BS, et al. Polypoidal choroidal vasculopathy and neovascularized age-related macular degeneration. Arch Ophthalmol 1999;117(11):1503–1510.
40. Sho K, Takahashi K, Yamada H, et al. Polypoidal choroidal vasculopathy: incidence, demographic features, and clinical characteristics. Arch Ophthalmol 2003;121(10):1392–1396.
41. Maruko I, Iida T, Saito M, et al. Clinical characteristics of exudative age-related macular degeneration in Japanese patients. Am J Ophthalmol 2007;144(1):15–22.
42. Smiddy WE. Economic implications of current age-related macular degeneration treatments. Ophthalmology 2009;116(3): 481–487.
43. Hernandez-Pastor LJ, Ortega A, Garcia-Layana A, Giraldez J. Cost-effectiveness of ranibizumab compared with photodynamic treatment of neovascular age-related macular degeneration. Clin Ther 2008;30(12):2436–2451.
44. Sasahara M, Tsujikawa A, Musashi K, et al. Polypoidal choroidal vasculopathy with choroidal vascular hyperpermeability. Am J Ophthalmol 2006;142(4):601–607.
45. Imamura Y, Fujiwara F, Margolis R, Spaide RF. Enhanced depth imaging optical coherence tomography of the choroid in central serous chorioretinopathy. Retina 2009;29(10): 1469–1473.
46. Ozawa S, Ishikawa K, Ito Y, et al. Differences in macular morphology between polypoidal choroidal vasculopathy and exudative age-related macular degeneration detected by optical coherence tomography. Retina 2009;29(6): 793–802.
47. Maruko I, Iida T, Sugano Y, et al. Subfoveal choroidal thickness after treatment of central serous chorioretinopathy. Ophthalmology 2010:117(9);1792–1799.

Fluorescein Staining of the Vitreous During Vitrectomy for Retinopathy of Prematurity

Vitreous staining using triamcinolone acetonide[1] or fluorescein[2] generally has been used even in children[3] to visualize the preretinal membrane and vitreous during vitrectomy.

During the surgery for retinopathy of prematurity (ROP), careful segmentation and extensive vitreous cutting are required around the base of tractional retinal detachments, vitreous base, and fibrovascular tissue.[4] Removal of the formed vitreous around the fibrovascular tissue and the vitreous base is a key factor for a successful surgery.[4] To remove the vitreous safely, good intraoperative visualization of the vitreous is essential.

In the current study, we included cases of aggressive posterior ROP in which wide-field vitrectomies are necessary to evaluate the staining of the entire vitreous. We describe a technique for staining the vitreous with fluorescein and compared it with staining using triamcinolone in these patients with ROP.

Patients and Methods

This study included 45 consecutive eyes with Stage 4A aggressive posterior ROP, which required vitrectomies with lensectomies to be performed in 30 babies (mean age, 24 weeks; range, 22–30 weeks); no infant had undergone a previous surgery. The same surgeon (N.A.) performed all the surgeries in our hospital between June 2005 and May 2008. All aspects of this study were approved by the institutional ethics committee, and the parents of the patients provided informed consent before the infants were enrolled in the study. The mean follow-up duration in the triamcinolone group was 32 months (range, 15–38 months), and in the fluorescein group, the mean follow-up duration was 28 months (range, 12–32 months).

From the Department of Ophthalmology, National Center for Child Health and Development, Tokyo, Japan.

The authors have no financial interest in any aspect of this report.

Reprint requests: Yuri Kobayashi, MD, Noriyuki Azuma, MD, PhD, 2-10-1 Okura Setagaya-ku, Tokyo, 157-8535, Japan; e-mail: azuma-n@ncchd.go.jp

The demographics of the study group are shown in Table 1. There was no difference in the severity of ROP between the two groups. All patients underwent a 3-port 25-gauge vitrectomy using a small contact lens designed for premature eyes. The other instruments, including infusion pipes, cannulas, and light pipes, were used as in the conventional 25-gauge system. We previously described the procedures of early vitreous surgery for ROP.[4,5] In 27 eyes of 18 patients, sodium intravenous fluorescein (0.1 mL/kg) was injected preoperatively for fluorescein angiography and to visualize the vitreous gel intraoperatively. The intervals between fluorescein angiography and vitrectomy ranged from 10 minutes to 20 minutes. When both eyes required surgery, the mean time to surgery in the other eye was approximately 50 minutes. In the other study group, 0.2 mL of triamcinolone was injected repeatedly into the vitreous cavity in 18 eyes of 12 patients to visualize the residual vitreous after lensectomy and core vitrectomy. The authors evaluated the staining pattern of the vitreous, the postoperative results, and any complications. Analyses were performed, and categorical differences were compared using Fisher's test. All P values were 2-sided, and $P < 0.05$ was considered statistically significant. Analyses were conducted using GraphPad Prism5.0 statistical software (GraphPad Prism Software Institute, La Jolla, CA).

Results

Injections of triamcinolone were required three to five times during the surgery because we could not achieve full visualization of the distance between the residual vitreous and the retinal surface; triamcinolone was only on the cut surface of the vitreous, and the vitreous gel beneath remained transparent. In contrast, fluorescein dye produced homogenous and full-thickness staining (Figure 1), especially around the fibrovascular tissue and the vitreous base (Figure 2), which was sufficiently stained green but remained transparent.

When fluorescein was used, an iatrogenic break occurred in 1 eye (3.7%) as a result of an unstable 25-gauge infusion cannula. The break was repaired by

Table 1. Demographic Characteristics of Eyes Undergoing Vitrectomy for Stage 4A ROP

Characteristic	Fluorescein Injection	Triamcinolone Injection
Number of eyes/patients	27/18	18/12
Gestational age, mean (range), weeks	24 (22–29)	25 (22–30)
Birth weight, mean (range), g	782 (366–1585)	834 (466–1,676)
Age at surgery, mean (range), weeks	15	14
Bilateral eyes	18	12
Zone of disease, eyes		
Zone	7	6
Posterior zone	16	8
Anterior zone	4	4
Extent of fibrous tissue, mean (range), cumulative clock hours	7.9 (1–12)	7.6 (2–12)

endophotocoagulation and fluid–gas exchange. When triamcinolone was used, 3 breaks (16.7%) occurred during cutting of the vitreous on the detached retina because of insufficient visualization.

Table 2 shows the postoperative reattachment rates at the final examination in each group. In the fluorescein group, the rate of complete retinal reattachment was 85%; in the triamcinolone group, the retinal reattachment rate was 67%. The retinas were partially reattached in 15% of the eyes in the fluorescein group and 26% of the eyes in the triamcinolone group. The average follow-up duration was 26 months (range, 15–37 months).

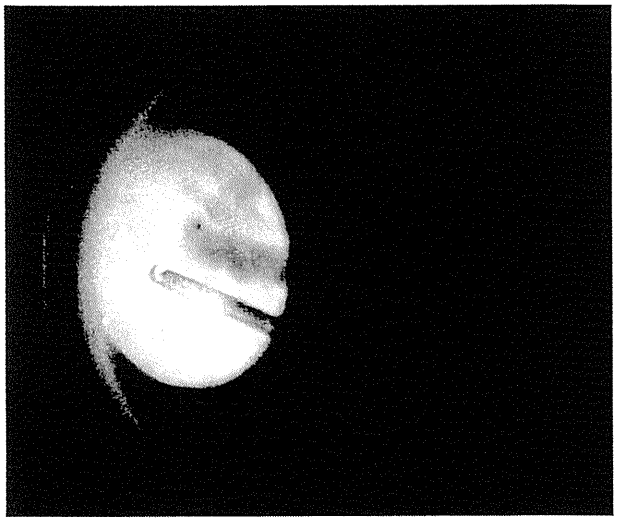

Fig. 1. Injection of fluorescein before vitrectomy to stain the vitreous in patients with Stage 4A ROP. The fluorescein is well distributed over the entire vitreous gel. The posterior vitreous cortex is clearly seen but remains transparent.

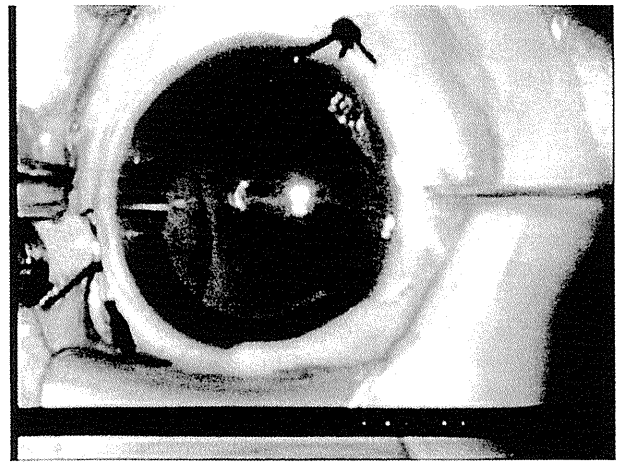

Fig. 2. The vitreous base is stained sufficiently, facilitating good visualization of residual vitreous.

There were no statistical differences between the two groups in the iatrogenic breaks ($P = 0.64 > 0.05$) and the reattachments rates at 18 months postoperatively ($P = 0.17 > 0.05$). No infants had systemic abnormalities intraoperatively or postoperatively. The degrees of postoperative inflammation were similar between the groups. No steroid-induced glaucoma developed postoperatively in the triamcinolone group.

Discussion

The current study suggested that fluorescein may be more useful than triamcinolone because fluorescein facilitated clear visualization around the vitreous base and the fibrovascular tissue. The base of the tractional retinal detachment was clearly visible and distinguishable from the retina, the fibrous tissue, and the stained peripheral vitreous, making cutting of the vitreous safer.

In the current study, there was no statistical significance between the groups possibly because of the small number of patients. However, an iatrogenic break in one eye stained with fluorescein resulted from the instability of the infusion cannula, and we assume that this break might have occurred during staining

Table 2. Postreattachment at Final Examination

	Triamcinolone Injection (n = 18 eyes)	Fluorescein Injection (n = 27 eyes)
Completely reattached, n (%)	12 eyes (67)	23 eyes (85)
Partially reattached, n (%)	4 eyes (22)	4 eyes (15)
Detached, n (%)	2 eyes (11)	0 eyes (0)
Follow-up (range), months	32 (15–38)	28 (12–32)

with either fluorescein or triamcinolone, which may not be related to the vitreous staining.

Three breaks occurred during cutting of the vitreous stained with triamcinolone, which seemed high; however, we had anticipated that cutting the vitreous without staining during the surgery for Stage 4A ROP would have resulted in more breaks than when using triamcinolone. In addition, the absence of staining would not have facilitated cutting of sufficient vitreous to achieve retinal reattachment in Stage 4A ROP because the solid and transparent vitreous adheres firmly to fibrovascular tissue, and it could not be separated from the retina especially at the vitreous base.

The use of triamcinolone in pediatric cases is controversial and may carry the risk of development of endophthalmitis and glaucoma, and the most common method of staining with triamcinolone in adults is direct injection into the vitreous.[1] However, fluorescein is an ophthalmic angiographic agent that leaks from fibrous tissue and then stains vitreous, and it is used in routine evaluations of patients with ROP.[5] Therefore, in the current study, we evaluated which agent was more suitable for this surgery.

No allergic reactions developed in any cases in which fluorescein was used, although such reactions in adults have been reported.[6] Therefore, these surgeries for ROP should be performed with the infants under carefully controlled general anesthesia. Compared with the use of triamcinolone, which required several vitreous injections into each eye, one intravenous injection of fluorescein eliminated complicated surgical procedures and reduced the risk of the development of endophthalmitis and glaucoma.

In addition, angiography confirmed the status and extent of the ROP preoperatively. Obtaining this information and a clear full-thickness view using fluorescein may reduce the incidence of iatrogenic dialysis and ensure successful surgeries.

Key words: retinopathy of prematurity, early vitreous surgery, fluorescein, staining, vitreous, triamcinolone acetonide.

YURI KOBAYASHI, MD
TAE YOKOI, MD
TADASHI YOKOI, MD
MIINA HIRAOKA, MD
SACHIKO NISHINA, MD, PHD
NORIYUKI AZUMA, MD, PHD

References

1. Matsumoto H, Yamanaka I, Hisatomi T, et al. Triamcinolone acetonide-assisted pars plana vitrectomy improves residual posterior vitreous hyaloid removal: ultrastructural analysis of the inner limiting membrane. Retina 2007;27:174–179.
2. Das T, Vedantham V. Intravitreal sodium fluorescein enhances visualization of clear vitreous during vitreous surgery for macular hole: a safety and efficacy study. Clin Experiment Ophthalmol 2004;32:55–57.
3. Lekhanpal RR, Fortun JA, Chank-kai B, Lensectomy and vitrectomy with and without intravitreal triamcinolone acetonide for vascularly active stage 5 retinal detachments in retinopathy of prematurity. Retina 2006;7:736–740.
4. Azuma N, Ishikawa K, Hama Y, Early vitreous surgery for aggressive posterior retinopathy of prematurity. Am J Ophthalmol 2006;142:636–643.
5. Nishina S, Yokoi T, Kobayashi Y, Effect of early vitreous surgery for aggressive posterior retinopathy of prematurity detected by fundus fluorescein angiography. Ophthalmology 2009;116:2442–2447.
6. LaPiana FG, Penner R. Anaphylactoid reaction to intravenously administered fluorescein. Arch Ophthalmol 1968;79: 161–162.

Clinical Features of Congenital Retinal Folds

SACHIKO NISHINA, YUMI SUZUKI, TADASHI YOKOI, YURI KOBAYASHI, EIICHIRO NODA, AND NORIYUKI AZUMA

• PURPOSE: To investigate the clinical features and prognosis of congenital retinal folds without systemic associations.

• DESIGN: Retrospective observational case series.

• METHODS: The characteristics, clinical course, ocular complications, and best-corrected visual acuity (BCVA) of eyes with congenital retinal folds were studied during the follow-up periods. The affected and fellow eyes were examined by slit-lamp biomicroscopy, binocular indirect ophthalmoscopy, and fundus fluorescein angiography. The parents and siblings of each patient also underwent ophthalmoscopic examinations. The BCVA was measured using a Landolt ring VA chart.

• RESULTS: One hundred forty-seven eyes of 121 patients with congenital retinal folds were examined. Fifty-five patients (45.5%) were female. The fold was unilateral in 95 patients (78.5%), and 69 of those patients (72.6%) had retinal abnormalities in the fellow eye. The meridional distribution of folds was temporal in 136 eyes (92.5%). The family history was positive in 32 patients (26.4%). Secondary fundus complications, including fibrovascular proliferation and tractional, rhegmatogenous, and exudative retinal detachments, developed in 44 eyes (29.9%). The BCVAs could be measured in 119 eyes and ranged from 20/100 to 20/20 in 5 eyes (4.2%), 2/100 to 20/200 in 45 eyes (37.8%), and 2/200 or worse in 69 eyes (58.0%). The follow-up periods ranged from 4 to 243 months (mean, 79.7 ± 58.9 months).

• CONCLUSIONS: These clinical features suggested that most congenital retinal folds may result from insufficient retinal vascular development, as in familial exudative vitreoretinopathy, rather than persistent fetal vasculature. Adequate management of active retinopathy and late-onset complications, especially retinal detachment, is required. (Am J Ophthalmol 2011;xx:xxx. © 2011 by Elsevier Inc. All rights reserved.)

A CONGENITAL RETINAL FOLD (ABLATIO FALCIFORmis congenital), extending radially from the optic disc toward the peripheral fundus, was first described in 1935 as a rare congenital anomaly.[1,2] The pathogenesis was investigated histologically, and the anomaly was hypothesized to be attributable to persistent hyaloid vessels leading to a pulled dysplastic retina. In 1955, Reese reported the clinical and pathologic features of persistent hyperplastic primary vitreous (PHPV).[3] In 1965, Michaelson[4] introduced the term "posterior PHPV,"[4] and in 1970 Pruett and Schepens[5] described a new clinical entity called "posterior hyperplastic primary vitreous," the posterior form of PHPV, characterized by vitreous membranes extending from the disc toward the peripheral fundus. Those investigators used the term posterior PHPV as a synonym for falciform retinal folds and the term anterior PHPV as a synonym for the PHPV described by Reese.[3] Thus, congenital retinal folds often were diagnosed as posterior PHPV afterward. The term PHPV now has evolved to persistent fetal vasculature (PFV), which usually occurs as a nonheritable set of vascular malformations affecting 1 eye of an otherwise normal infant.[6] However, based on the fundus drawings of Pruett and Schepens,[5] vitreous membranes and retinal folds were not clearly distinguished. Those authors reported that the vitreous band and retinal folds extended toward the fundus periphery in various meridians but were most commonly nasal.[5] They also described the pleomorphism of posterior PHPV and complications such as microcornea, retinal detachment, vitreous hemorrhage, cataract, and glaucoma.[7] In most cases, posterior PHPV is unilateral and rarely familial.

In 1969, familial (dominant) exudative vitreoretinopathy (FEVR), a developmental disorder of the retinal vasculature, was described and suggested to be the possible origin of congenital retinal folds.[8–10] Recently, congenital retinal folds were thought to occur even after birth and were caused by various infantile diseases such as FEVR, retinopathy of prematurity (ROP), Norrie disease, incontinentia pigmenti, and congenital toxoplasmosis. However, clinically distinguishing retinal folds without systemic associations is often difficult, and their pathogenesis remains controversial.

We conducted the current study to clarify the clinical features of congenital retinal folds without systemic associations.

METHODS

ONE HUNDRED FORTY-SEVEN EYES OF 121 PATIENTS WITH unilateral or bilateral congenital retinal folds, diagnosed at the National Center for Child Health and Development,

Accepted for publication Jun 6, 2011.

From the Division of Ophthalmology, National Center for Child Health and Development, Tokyo, Japan.

Inquiries to Noriyuki Azuma, Division of Ophthalmology, National Center for Child Health and Development, 2-10-1 Ohkura, Setagaya-ku, Tokyo, 157-8535, Japan; e-mail: azuma-n@ncchd.go.jp

0002-9394/$36.00
doi:10.1016/j.ajo.2011.06.002