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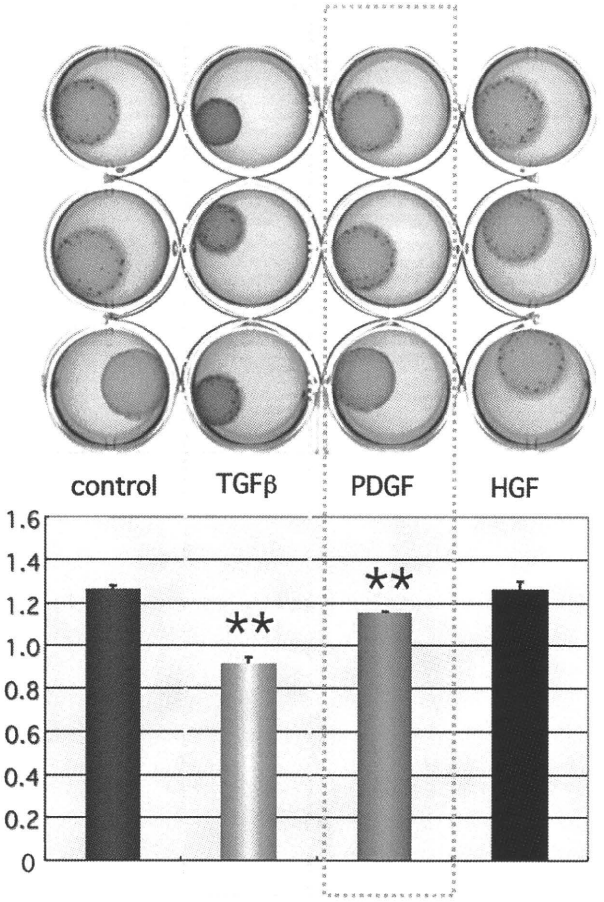

Fig. 4. Contraction of collagen gel embedded with hyalocytes. A collagen gel embedded with hyalocytes was stimulated with cytokines, such as TGF-β, platelet-derived growth factor (PDGF), or hepatocyte growth factor (HGF), and the size of the collagen gel was measured after 24 hours. The contraction of gel was significantly enhanced by TGF-β or PDGF (**$P < 0.01$). Reproduced with permission from Sakamoto.[10]

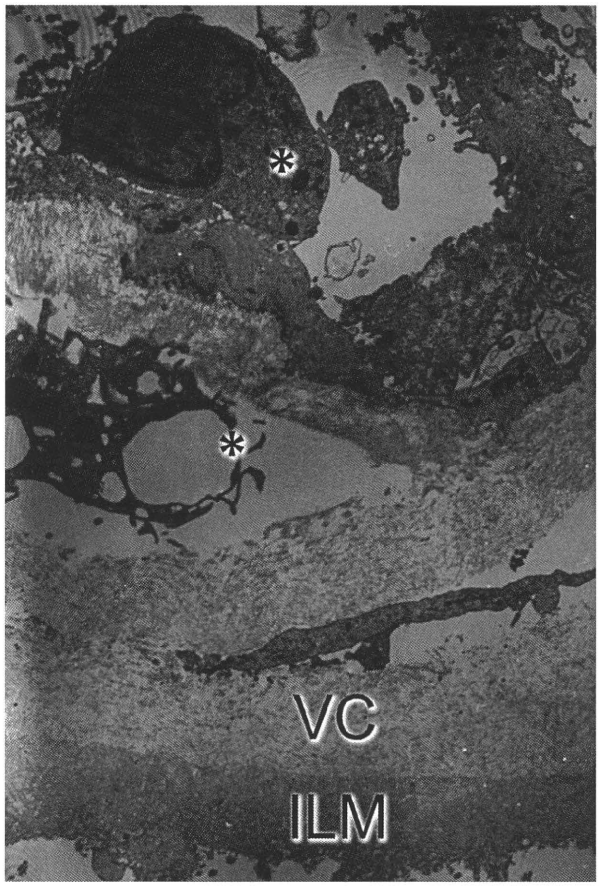

Fig. 5. Transmission electron microscopic photograph of surgically removed internal limiting membrane (ILM) from the eye of ERM. Macrophage-like cells (*) are present on the vitreous cortex (VC) and ILM. They are presumably hyalocytes. Reproduced with permission from Sakamoto[10] (original magnification, ×1800).

maneuver itself is not necessarily easy and recurrence is not rare. Adjunctive use of triamcinolone acetonide in vitrectomy is beneficial to remove these membranes securely and effectively.[53,54] Although this procedure is not always necessary in most of the cases, it might be beneficial for selected cases to reduce the incidence of postoperative preretinal fibrotic complications.[54] Complete removal of ERM together with internal limiting membrane resulted in a lower recurrence rate than incomplete removal, probably because the residual hyaloid or membrane becomes a scaffold of cell proliferation and ECM production by these cells.[55] If the residual hyaloid or internal limiting membrane is left alone without any cells, recurrence, namely reproduction of ECM by cellular elements after surgery, will not occur.

There are novel pharmacologic approaches to the disease. In an in vitro study, Rho and ROCK were found to play an important role in phosphorylation of the myosin light chain and the subsequent contraction; thus, a specific Rho kinase (ROCK) inhibitor fasudil could block contraction of collagen gel embedded with hyalocytes.[36] In rabbits, fasudil significantly inhibited the progression of experimental proliferative vitreoretinopathy without affecting the viability of retinal cells. ROCK, a key downstream mediator of TGF-β and other factors, might become a unique therapeutic target.[36] Of course, there is a distance between an animal study and the bedside; however, a pharmacologic approach to modulate hyalocytes might be a novel treatment of intraocular diseases.

Summary

As described above, there is no strict definition of "hyalocytes," but cells located at the periphery of vitreous cavity are called hyalocytes. The accumulating evidence shows that these hyalocytes can act as

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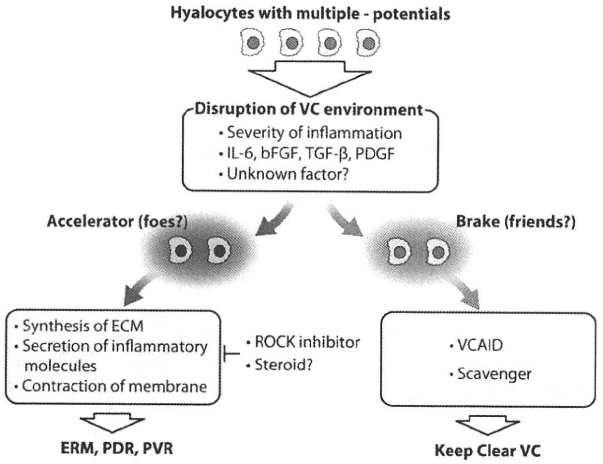

Fig. 6. Schema of possible roles of hyalocytes in ocular pathology. Hyalocytes are residual cells in vitreous cavity (VC) with multiple potentials. In the disruption of the VC environment, hyalocytes may act as an accelerator or a brake to destroy the clear vitreous dependent on unknown mechanisms. IL-6, interleukin-6; bFGF, basic fibroblast growth factor; PDGF, platelet-derived growth factor; PDR, proliferative diabetic retinopathy; PVR, proliferative vitreoretinopathy.

"friends" to keep the vitreous cavity clear by inhibiting immune reaction through vitreous cavity–associated immune deviation. At the same time, hyalocytes can act as "foes" by producing inflammatory cytokines and ECM followed by contraction of the membrane. Unfortunately, at present, it is difficult to tell what makes hyalocytes "friends" or "foes" (Figure 6). Further studies to answer this question might provide a key to a better understanding of microenvironment of the vitreous cavity and to developing an effective treatment for intraocular diseases.

F6

Key words: antigen-presenting cells, fibronectin, macular edema, VCAID, vitrectomy.

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Results of One-Year Follow-Up Examinations after Intravitreal Bevacizumab Administration for Chronic Central Serous Chorioretinopathy

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Key Words
Central serous chorioretinopathy · Bevacizumab · Serous retinal detachment · Pigment epithelium detachment

Abstract
Background: Our purpose was to report the results of 1-year follow-up examinations after intravitreal bevacizumab injection for the treatment of chronic central serous chorioretinopathy (CSC). ***Methods:*** Five eyes in 5 patients with chronic CSC were intravitreally injected with 1.25 mg/0.05 ml of bevacizumab. The need for retreatment was evaluated if spectral-domain optical coherence tomography showed the presence of subretinal fluid at the time of a 1-month follow-up examination. Best-corrected visual acuity and central foveal thickness were compared between baseline and 1 year after the first injection. ***Results:*** The mean logarithm of the minimum angle of resolution (logMAR) best-corrected visual acuity improved from 0.23 ± 0.46 to 0.17 ± 0.47 and the mean central foveal thickness significantly decreased from 323 ± 98 μm to 171 ± 63 μm ($p < 0.05$). ***Conclusion:*** The intravitreal injection of bevacizumab is well tolerated in maintaining vision and reducing serous retinal detachment in patients with chronic CSC, as evaluated at a 1-year follow-up examination.

Introduction

Central serous chorioretinopathy (CSC) is characterized by a serous neurosensory detachment of the central macula associated with idiopathic leakage at the level of the retinal pigment epithelium (RPE) [1]. It is reported that CSC is a benign and self-limited disease which shows spontaneous resolution of a neurosensory elevation [2]. However, there exist some cases continuing with persistent pigment epithelial detachment (PED) and subretinal fluid, which means chronic CSC. Chronic CSC can cause RPE atrophy and photoreceptor degeneration, resulting in irreversible functional and anatomical damage [3–5].

The cause of CSC has been reported to be associated with choroidal vascular hyperpermeability [6]. Therefore, preventing the hyperpermeability of the choroidal vessels may play an important role for the treatment of CSC. Bevacizumab, a recombinant humanized monoclonal antibody to inhibit vascular endothelial growth factor (VEGF), is expected to reduce a serous neurosensory detachment caused by CSC. However, studies examining the use of intravitreal bevacizumab for CSC are rare, and none of the patients in these reports were followed for >1 year.

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Table 1. Baseline characteristics and clinical data before and after bevacizumab injection

Patient	Age in years	Gender	Best-corrected visual acuity				Central foveal thickness, μm					Injections	Period of recurrence, months
			baseline	month 3	month 6	month 12	baseline	month 3	at recurrence	month 6	month 12		
1	55	M	20/25	20/25	20/25	20/25	225	138	–	118	120	1	–
2	44	F	20/16	20/20	20/16	20/16	461	272	372	263	242	4	4
3	37	M	20/200	20/200	20/200	20/200	386	140	–	111	93	1	–
4	52	M	20/25	20/16	20/16	20/16	270	249	–	160	211	1	–
5	42	M	20/20	20/16	20/16	20/16	272	225	240	150	191	2	5
Mean ± SD	46 ± 7.4		0.23 ± 0.46	0.20 ± 0.48	0.17 ± 0.47	0.17 ± 0.47	323 ± 98	205 ± 62	–	160 ± 61	171 ± 63		

SD = Standard deviation. Mean best-corrected visual acuity was converted to logMAR equivalents.

The purpose of this study was to analyze the 1-year results of intravitreal bevacizumab administration for the treatment of chronic CSC.

Patients and Methods

A prospective interventional study was designed to evaluate the safety and efficacy of intravitreal bevacizumab (Avastin; Genentech, Inc., San Francisco, Calif., USA) for the treatment of chronic CSC. The study was approved by the institute committee. We studied 5 eyes in 5 patients with chronic CSC who had had symptoms for >6 months or who had a recurrent history of CSC and followed these patients for ≥12 months after the first intravitreal administration of bevacizumab. All patients were treated at Yokohama City University Medical Center between August 2008 and December 2009. None of the patients had previously received any other treatments. The visual acuity at baseline was better than 20/25 in 4 patients. However, they presented with decreased visual acuity or metamorphopsia. Therefore, intravitreal bevacizumab injection was chosen to improve their symptoms. Informed consent was obtained from all the eligible patients. The ethics standards of the Declaration of Helsinki were followed.

Best-corrected visual acuity (BCVA) measurements and spectral-domain optical coherence tomography (SD-OCT, Cirrus high-definition OCT; Carl Zeiss, Dublin, Calif., USA) imaging were performed in all patients before and after the injection at monthly intervals. The central foveal thickness (CFT) was measured using SD-OCT. The BCVA was converted to logarithm of the minimum angle of resolution (logMAR) equivalents for statistical analysis. Fluorescein angiography and indocyanine green angiography were also performed before the first injection.

All the patients received 1.25 mg/0.05 ml of bevacizumab via an intravitreal injection through the pars plana using a 30-gauge needle at baseline. The injection was repeated if SD-OCT showed the presence of subretinal fluid at a 1-month follow-up examination by the evaluating physician [7]. The main outcome measures were BCVA and CFT, as documented using SD-OCT.

Mann-Whitney's U test was used to compare the data. All analyses were conducted with the SPSS software package (SPSS Inc., Chicago, Ill., USA). A value of $p < 0.05$ was considered statistically significant.

Results

The baseline characteristics and clinical data before and after bevacizumab injection are shown in table 1. All eyes were assessed at a 1-year follow-up examination. Of the 5 patients included in the series, 4 were men and 1 was a woman. The patient age ranged from 37 to 55 years (mean age = 46 ± 7.4 years). All eyes had serous retinal detachment (SRD), and 3 eyes had PED at baseline.

The mean logMAR visual acuity before treatment was 0.23 ± 0.46. At 3, 6 and 12 months after the first injection, the mean logMAR BCVA values were 0.20 ± 0.48, 0.17 ± 0.47 and 0.17 ± 0.47, respectively. A BCVA improvement from baseline was shown, although these values were not significantly different from baseline.

On the other hand, the mean CFT significantly decreased from 323 ± 98 μm at baseline to 171 ± 63 μm at the 1-year follow-up examination ($p < 0.05$).

SRD or PED was reduced in all eyes after the first injection (fig. 1) but slightly recurred in 2 eyes at follow-up. Recurrence developed at 4 months after the first injection in patient 2 (table 1). Patient 5 also recurred 5 months after baseline. A second injection was given to the patients, and SRD was reduced completely over the 1-year follow-up. No significant ocular or systemic adverse effects occurred.

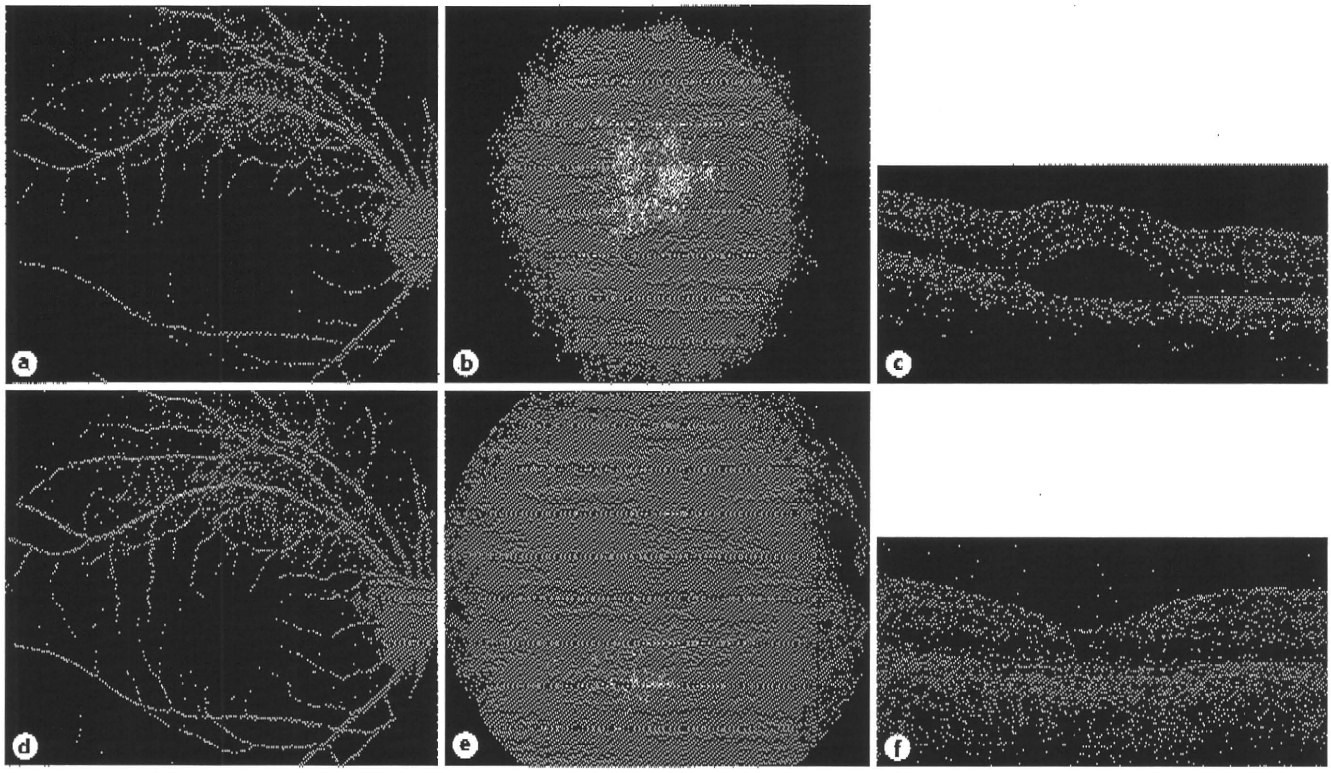

Fig. 1. Patient 1 in table 1, a 55-year-old man, presented with a diminution of visual acuity and metamorphopsia in his right eye. A late-phase image of fluorescein angiography showed a focal leakage (**a**); mid-phase indocyanine green angiography confirmed hyperfluescence compatible with leakage on fluorescein angiography (**b**); SD-OCT also revealed presence of SRD including the fovea (**c**); 1-month follow-up examinations after the first injection in patient 1. A late-phase image of fluorescein angiography showed the resolution of leakage (**d**); mid-phase indocyanine green angiography revealed decrease in hyperfluesce (**e**); SD-OCT demonstrated the absence of subretinal fluid (**f**).

Discussion

Similarly to previously case series [8–11], our study demonstrated that intravitreal injection of bevacizumab was effective for stabilizing vision and improving SRD and PED in patients with chronic CSC in a 1-year follow-up examination. In all previous reports, the mean follow-up periods were relatively short [8–11]. Few trials have had a follow-up period of 1 year.

Various treatments for CSC, including the use of medication [12–15], transpupillary thermotherapy [16, 17] and surgery [18], have been studied. However, no optimal treatment for CSC has been determined. At present, laser photocoagulation is the most frequently used treatment for CSC, but it often leaves scotoma and is associated with subsequent development of secondary choroidal neovascularization. Recently, photodynamic therapy with verteporfin, which has been proven to be effective for secondary choriodal neovascularization resulting from aged-related macular degeneration [19], has also been reported to be well tolerated for chronic CSC [20, 21], although damage to the RPE, severe choroidal ischemia and subsequent secondary choroidal neovascularization were observed after photodynamic therapy for the treatment [21–24].

The pathogenesis of CSC has been reported to be associated with choroidal vascular hyperpermeability by using indocyanine green angiography [6]. Recently, the thickness of the choroid in eyes with CSC was shown to be greater than in normal eyes, which supported that increased hydrostatic pressure in the choroid might cause CSC [25]. Therefore, focusing on the hyperpermeability of the choroidal vessels may play an important role for the treatment of CSC. VEGF is a potent inducer of vascular permeability [26]. Therefore, we speculated that bevacizumab, a full-length VEGF antibody, might be effective for reducing neurosensory detachment and develop with encouraging results. Furthermore, our study showed no severe adverse effects during the follow-up period.

In our study, the mean logMAR BCVA improved from 0.23 ± 0.46 to 0.17 ± 0.47. Since the sample size was small, these values were not significantly different from baseline. However, their visual acuity at 1 year was comparatively better than when injected at baseline. Therefore, we assess that bevacizumab is useful for improving the visual and anatomical function for chronic CSC during a 1-year follow-up period.

In 2 patients, SRD slightly recurred at the follow-up examination. A similar report has shown slight recurrence during the follow-up period by using bevacizumab injection in patients with chronic CSC [10]. Based on the pharmacokinetics of intravitreal bevacizumab, the minimum concentration completely blocking the VEGF could be maintained for 48 days [27]. Simple injection of bevacizumab may result in limited effects because it is difficult to maintain a sufficient level of intravitreal bevacizumab. Therefore, further investigation is needed to determine an appropriate protocol for bevacizumab injection for chronic CSC.

In conclusion, intravitreal injection of bevacizumab is well tolerated in maintaining vision and reducing SRD or PED for chronic CSC, as evaluated at a 1-year follow-up examination. However, simple injection of bevacizumab may result in limited effects. Further investigations are needed to assess the long-term safety and the best protocol for the efficacy of intravitreal bevacizumab.

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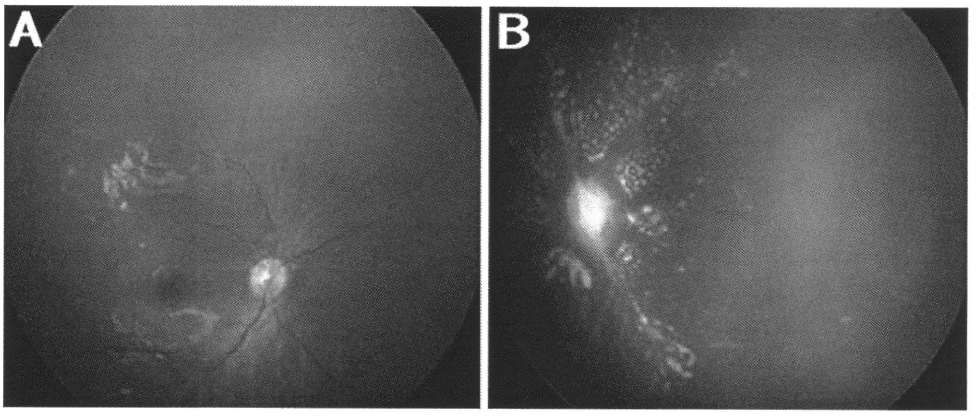

Figure 2A, B. Fundus photographs of the **A** right and **B** left eyes 1 month after administration of fluconazole. **A** The size of the white lesions had decreased significantly. **B** Retinal reattachment with hard exudates, white vessels, and optic disc pallor were observed.

in a patient with *Candida* vaginitis and onychomycosis; both patients were treated with antibiotics.[2,3] The current patient had no systemic abnormalities but evidently had endogenous *Candida* endophthalmitis because PCR analysis detected sufficient quantities of *Candida* DNA in the vitreous and the cerebrospinal fluid to diagnose the infection. FA findings of abnormal vasculature in the peripheral retina are usually seen in eyes with retinopathy of prematurity or familial exudative vitreoretinopathy, which prompted us to suspect that the *Candida* infection in the present case was congenital. Generally, a congenital *Candida* infection occurs by vertical transmission through the uterus or vagina and is associated with systemic involvement, including dermatitis, meningitis, anomaly of the brain, and oral mucositis.[4] However, the patient was delivered by Caesarean section, and no signs of *Candida* infection were detected in the mother. Thus, acquired *Candida* infection was the most likely diagnosis in the present case. Intravenous antibiotics delivered 2 weeks before the onset of bilateral endophthalmitis likely caused iatrogenic *Candida* infection because of inadvertent manipulation. Possible insufficient growth of the retinal vasculature might have facilitated the proliferation of *Candida* in the patient's retina.

To diagnose and treat such a difficult case, broad-range PCR for the 18S ribosomal RNA sequence is a good screening tool.[5] Moreover, real-time PCR can examine the quantity of the pathogen and determine its relation to the endophthalmitis. Early treatment of infectious endophthalmitis is essential in infants, in whom vision develops rapidly. Thus, a broad-range, real-time PCR system using ocular samples is useful when the patient has uveitis or endophthalmitis of unknown origin.

Keywords: *Candida* chorioretinitis, *Candida* infection, polymerase chain reaction

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Choroidal Neovascularization in a Child Following Laser Pointer-Induced Macular Injury

Laser pointer-induced macular injury is characterized by a decrease in visual acuity and metamorphopsia.[1] High-energy lasers can cause chorioretinal damage, which can lead to choroidal neovascularization (CNV) in animals.[2] Case reports of the development of a CNV following laser-induced macular injury have also been published.[3,4] We report the case of a child with a CNV that developed following a macular injury caused by repeated exposure to a green laser pointer. The prevalence of CNV in children is low, but it is still an important cause of visual impairment.[5] To the best of our knowledge, this is the first report of a child developing CNV following a macular injury caused by exposure to a green laser pointer.

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Case Report

An 11-year-old boy with decreased visual acuity in the right eye was referred to our hospital for consultation. The parents reported that the child stared directly at a commonly used green laser pointer. He did not understand the cautionary statement, and from the age of 2 to 3 years stared at it with his dominant right eye every day for more than 10 s at a time, as if it were a toy, at a distance of 30 cm. Although he had a congenital hearing loss and mental retardation, his visual functions developed normally up to the time of the injury. When he was 7 years old, his visual acuity was 1.0 OU, after correction of bilateral astigmatism, –4.0 diopters.

When he was 11 years old, his best-corrected visual acuity (BCVA) was 0.2 OD and 1.0 OS. No abnormalities were found in the anterior segment of either eye. Ophthalmoscopy identified a yellow exudate-like lesion or fibrous tissue surrounded by subretinal hemorrhage in the right macula (Fig. 1A). The left eye was completely normal. Two years later when he was 13 years of age, the fundus showed a yellow fibrous lesion in the right macula (Fig. 1B) that demonstrated leakage on fluorescein angiography (Fig. 1C, D). A STRATUS optical coherence tomography image showed a highly reflective mass that extended from the outer retinal layer through the retinal pigment epithelium and Bruch's membrane into the choroidal tissue of the right macula (Fig. 1E). The left eye was normal. Investigations for ocular infectious diseases did not reveal any disease.

We elected to follow the patient with careful observation and not to perform invasive therapy because of his age and mental condition. He is now 14 years old, and his BCVA and the appearance of the fibrous tissue are unchanged.

Comment

By the results of the ophthalmological examinations and the history of events, we diagnosed the patient as having laser pointer-induced macular injury. An accurate diagnosis of laser pointer-induced macular injury did not come easily, because it was difficult to interpret the complaints of the

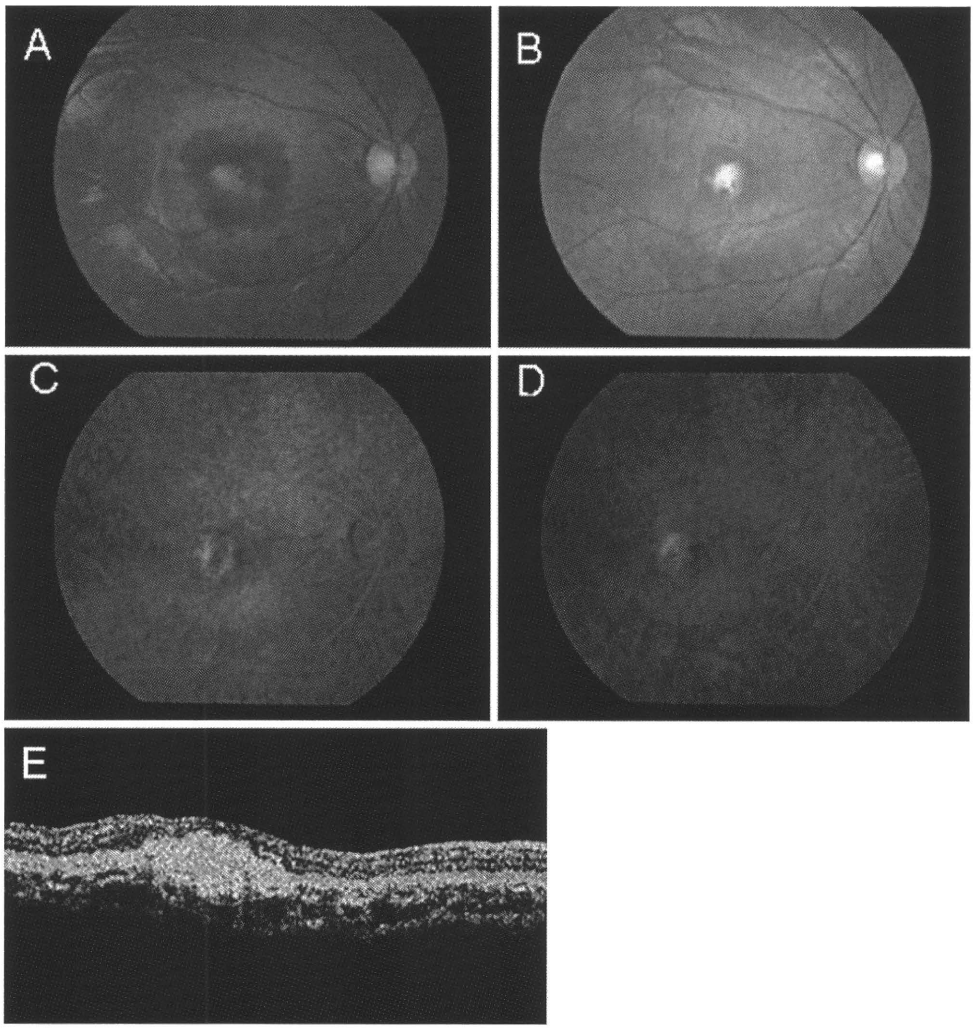

Figure 1A–E. Fundus images of the current case. **A** When the patient was 11 years old, the fundus of his right eye showed a yellow lesion resembling exudates or fibrous tissue surrounded by subretinal hemorrhage in the macula. **B** When he was 13 years old, the fundus showed a yellow lesion resembling fibrous tissue. **C, D** Fluorescein angiography showed leakage with fibrous tissue remaining in the right macula (**C** early phase; **D** late phase). **E** Optical coherence tomography demonstrated a highly reflective mass extending not only to the outer retinal layer and retinal pigment epithelium but also to the Bruch's membrane and choroidal tissue.

patient, and the time of the injury and initial examination were prolonged.

There is a correlation between the energy of a laser and the degree of chorioretinal damage it can cause. The output power of handheld laser pointers is commonly from 1 to 5 mW. Mild thermal retinal injuries might be caused by a 5-mW laser, if it is stared at for more than 10 to 20 s;[1] this suggests that the chorioretinal damage in our patient, which probably induced the CNV, was caused by the frequent and repeated exposure to the low-energy laser beam.

The prognosis of this patient is unclear, because the interval between the first laser exposure and the development of the CNV was long in comparison to previously reported cases. The patient is being carefully followed for the possible reactivation of the CNV.

Keywords: choroidal neovascularization, laser pointer, macular injury

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Spontaneous Closure of a Stage 2 Macular Hole Without Detachment of the Posterior Hyaloid

Stage 2 macular holes occasionally close spontaneously after hyaloid membranes with pseudo-opercula become separated from the surface of the retina. However, we observed spontaneous closure of a stage 2 macular hole without release of the vitreofoveal traction. This case was documented by means of optical coherence tomography (OCT).

Case Report

A 52-year-old man complained of metamorphopsia in his left eye. He was referred to a nearby clinic, and a macular hole in the left eye was diagnosed. He did not report any trauma. About 2 weeks later, he came to our clinic at Akita University Hospital. His best-corrected visual acuity was 20/16 in the right eye and 20/160 in the left. Slit-lamp examination showed no remarkable findings. Biomicroscopic examination did not reveal posterior vitreous detachment (PVD). OCT (Zeiss OCT3; Zeiss-Humphrey Systems, Dublin, CA, USA) showed the presence of a stage 2 macular hole with perifoveal cyst formation (Fig. 1A). The hole measured 336 μm in diameter and was partially covered with a retinal flap. A posterior hyaloid was present and adhered to the edge of the hole (Fig. 1B). Around the macular hole, there was a shallow PVD. He did not have any other ocular diseases such as diabetic retinopathy, retinal vein occlusion, macular telangiectasia, or uveitis.

Four months later, the patient's best-corrected visual acuity had improved to 20/30. OCT seemed to show the presence of an outer retinal bridge over the macular hole (Fig. 1C, D), indicating a spontaneous macular hole closure in process. The perifoveal cysts were no longer apparent. However, the patient still felt metamorphopsia in his left eye, and the posterior hyaloid remained adhered to the retinal flap (Fig. 1E). To release this adhesion and close the hole completely, we performed a pars plana vitrectomy. During the operation, we used triamcinolone acetonide to visualize the vitreous and observed the hyaloid attachment to the macular hole. We did not peel the internal limiting membrane because the macular hole was already bridged and we thought that releasing the attachment was sufficient to close the hole completely. At the end of the operation, air tamponade was used.

Seven days after the surgery, OCT showed the presence of a thick bridge and a well-defined retinal hyporeflective space interrupting the inner high-reflective layer (Fig. 2A). Seven months after surgery, the patient's best-corrected visual acuity remained at 20/30. The hyporeflective space had become quite small. Two and a half years after surgery, his best-corrected visual acuity was 20/20. OCT (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany) showed that the hyporeflective space no longer existed and the foveal morphology had progressed to almost normal (Fig. 2B).

Comments

As the use of OCT has become more common, many cases of spontaneous closure of macular holes have been reported.[1–4] Four explanations have been proposed for the

Risk Factors for Recurrent Fibrovascular Proliferation in Aggressive Posterior Retinopathy of Prematurity After Early Vitreous Surgery

TADASHI YOKOI, TAE YOKOI, YURI KOBAYASHI, SACHIKO NISHINA, AND NORIYUKI AZUMA

• PURPOSE: To analyze risk factors for postoperative recurrence of fibrovascular tissue in eyes with aggressive posterior retinopathy of prematurity (AP ROP) treated with early vitreous surgery.

• DESIGN: Retrospective, consecutive, observational case series.

• METHODS: Thirty-one patients (50 eyes) with AP ROP who underwent early vitreous surgery between March 2005 and April 2008 participated. Eyes with stage 4A or 4B disease in which fibrovascular tissue was not attached to the vitreous base were included; those in which fibrovascular tissue was attached extensively to vitreous base or those without dense photocoagulation to the nonvascularized retina were excluded. Eligible eyes were divided into 2 groups based on postoperative recurrence or no recurrence of fibrovascular tissue. Data on gender, gestational age, birth weight, Apgar score, intubation duration, severe systemic complications, preoperative ROP stage, zone, fibrovascular tissue and vitreous base adhesion, clock hours of fibrovascular tissue, postmenstrual age at the initial application of dense photocoagulation, dense photocoagulation to both vascularized and nonvascularized retina, postmenstrual age at vitrectomy, and intraoperative hemorrhage were collected and analyzed.

• RESULTS: Fifty eyes of 31 patients underwent early vitrectomy. Seven (14%) eyes were excluded and 43 eyes (86%) were included. Eight (18%) of 43 eyes had a recurrence of fibrovascular tissue. Both univariate and multivariate analysis indicated application of dense photocoagulation to both the vascularized and nonvascularized retina was a significant factor in the decreased recurrence of fibrovascular tissue ($P = .002$ and $P = .008$, respectively).

• CONCLUSIONS: Application of preoperative dense photocoagulation to vascularized and nonvascularized retina may be important for lowering the recurrence of fibrovascular tissue in eyes with AP ROP. (Am J Ophthalmol 2010;150:10–15. © 2010 by Elsevier Inc. All rights reserved.)

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AGGRESSIVE POSTERIOR RETINOPATHY OF PREMATURITY (AP ROP) is characterized by posterior retinopathy usually in zone I, substantial dilatation and tortuosity of the vessels at the posterior pole, a flat network of neovascularization on the retinal surface, circumferential fibrovascular tissue extending for 12 clock hours, and rapid progression to stage 5 without the classic course that includes stages 1 through 3.[1] Previous randomized trials have reported that application of photocoagulation to the nonvascularized retina prevents retinal detachment in classic ROP, but that photocoagulation often cannot prevent progression in eyes with AP ROP.[2]

Because the visual prognosis is poor after vitrectomy performed when AP ROP progresses to stage 5,[3,4] several early surgical interventions have been tried to prevent stage 5 retinal detachment. Scleral buckling that reduces the traction between the fibrovascular tissue and the retina is ineffective for AP ROP that is characterized by fibrovascular tissue nearly 360 degrees circumferentially in the posterior retina.[5–8] Lens-sparing vitrectomy usually is successful if performed for tractional retinal detachment in eyes with classic ROP, but the surgery is unsuccessful for AP ROP.[9] Although it is controversial whether lensectomy is necessary during vitrectomy to treat retinal detachment in eyes with AP ROP,[10,11] wide-field vitrectomy with lensectomy may be required to treat retinal detachment in eyes with AP ROP, which always is characterized by high disease activity despite the disadvantages of lens removal.

Eyes with AP ROP that have undergone early vitrectomy often have a retinal reattachment;[9] however, among these eyes, we recently identified eyes in which proliferation of fibrovascular tissue recurred after surgery. Because a very low birth weight, young gestational age, or long-term high oxygen therapy are risk factors for severe ROP,[12–14] we analyzed the correlation between recurrent fibrovascular tissue proliferation after early vitrectomy and the associated risk factors.

METHODS

THE MEDICAL RECORDS OF ALL EYES THAT UNDERWENT early vitrectomy with lensectomy[9] for stage 4 ROP associated with AP ROP were reviewed retrospectively at the Department of Ophthalmology, National Center for Child

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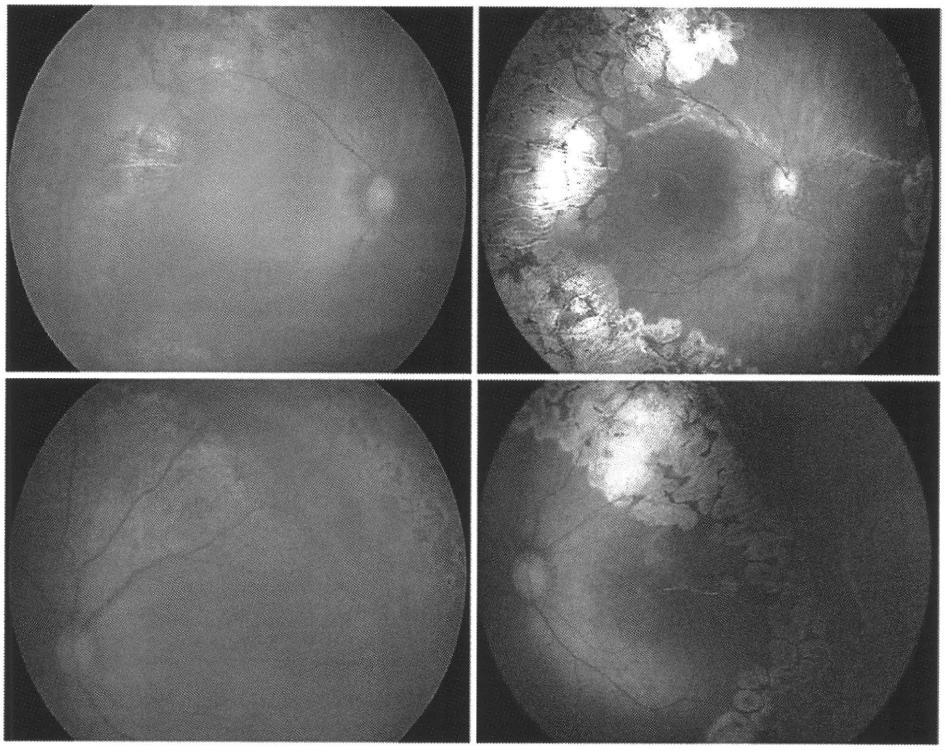

FIGURE 1. Fundus photographs of aggressive posterior retinopathy of prematurity in eyes of patients who underwent early vitreous surgery and preoperative photocoagulation to both the vascularized and nonvascularized retina. (Top left and Bottom left) Fundus photographs obtained before surgery showing densely applied photocoagulation in both the nonvascularized retina and the vascularized retina 3 to 4 spots posterior to the junction. Fibrovascular tissue and a focal tractional retinal detachment are seen at the junction. (Top right and Bottom right) Fundus photographs obtained 4 months after surgery showing that the retinopathy has been treated successfully without recurrence of fibrovascular tissue.

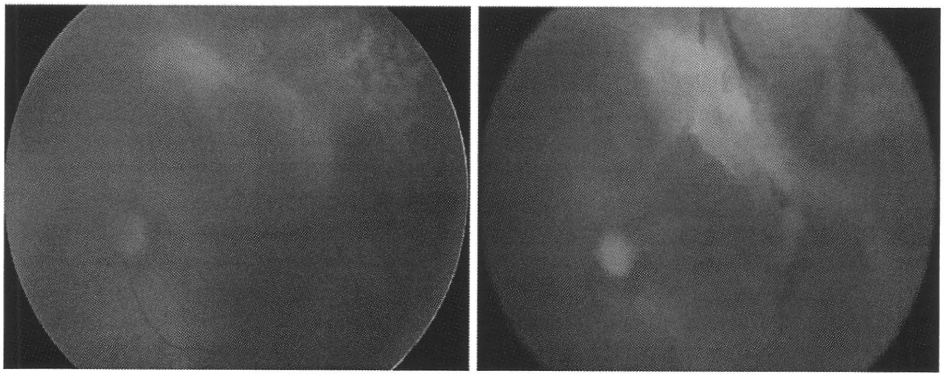

FIGURE 2. Fundus photographs of aggressive posterior retinopathy of prematurity in the left eye of a patient who underwent early vitreous surgery and preoperative photocoagulation to the nonvascularized retina. (Left) Fundus photograph obtained before surgery showing that photocoagulation was applied to the nonvascularized retina. Reddish fibrovascular tissue and a tractional retinal detachment are observed at the junction. (Right) Fundus photograph obtained 1 month after surgery showing recurrence of fibrovascular tissue in the posterior vascularized retina with a traction retinal detachment.

Health and Development, Tokyo, Japan, from March 2005 through April 2008. All eyes with AP ROP were diagnosed at the referring hospital or our institution based on the description published in 2005.[1] Eyes with stage 4A or stage 4B ROP in which fibrovascular tissue did not reach the vitreous base[9] were included; eyes with fibrovascular tissue attached extensively to the vitreous base or eyes without dense and early application of photocoagulation even to the nonvascularized retina were excluded, because those eyes usually have a stage 5 retinal detachment, and rigorous evaluation of

TABLE. Univariate Analysis between Baseline Demographics and Recurrence in the Eyes with Aggressive Posterior Retinopathy of Prematureity after Early Vitreous Surgery

	Total (n = 43)	Recurrence after Early Vitreous Surgery		*P* Value (2-Tailed)
		Yes (n = 8; 19%)	No (n = 35; 81%)	
Baseline characteristics				
No. eyes/patients	43/29	8/6	35/25	
Male, no (%)	13 (30.2)	5 (62.5)	8 (22.9)	.042[a]
Gestational age (wks), mean ± SD	25.1 ± 2.3	24.8 ± 2.0	25.2 ± 2.4	.703[b]
Birth weight (g) mean ± SD	808.7 ± 369.6	789.5 ± 302.2	813.0 ± 387.0	.873[b]
Apgar score at 5 min, median (range)	6 (1 to 10)	6 (2 to 10)	5 (1 to 10)	.311[c]
Intubation duration (wks), mean ± SD	57.0 ± 40.6	60.9 ± 49.2	56.1 ± 39.2	.767[b]
Severe systemic complication, no. (%)	12 (27.9)	2 (25.0)	10 (28.6)	>.99[a]
Follow-up (mos), mean ± SD	23.8 ± 10.7	22.6 ± 7.8	24.1 ± 11.3	>.99[b]
ROP findings				
Zone, no. (%)				.404[a]
1	29 (67.4)	4 (50.0)	25 (71.4)	
2	14 (32.6)	4 (50.0)	10 (28.6)	
Stage, no. (%)				.067[a]
4A	37 (86.0)	5 (62.5)	32 (91.4)	
4B	6 (14.0)	3 (37.5)	3 (8.6)	
Fibrovascular tissue and vitreous base adhesion, no. (%)	5 (11.6)	3 (37.5)	2 (5.7)	.037[a]
Clock hours of fibrovascular tissue, median (range)	5 (2 to 12)	9 (2 to 12)	5 (2 to 12)	.344[c]
PMA (wks) at initial PHC, mean ± SD	32.9 ± 1.8	32.1 ± 0.8	33.1 ± 1.9	.180[b]
Interval between initial PHC and virectomy (wks), mean ± SD	6.9 ± 3.2	7.0 ± 2.6	6.3 ± 3.3	.892[b]
PMA (wks) at vitrectomy, mean ± SD	39.7 ± 3.1	39.1 ± 2.9	39.2 ± 3.9	.536[b]
Intraoperative hemorrhage, no. (%)	13 (30.0)	3 (37.5)	10 (28.6)	>.99[a]
PHC to both vascularized and nonvascularized retina, no. (%)	27 (62.8)	1 (12.5)	26 (74.3)	.002[a]

mos = months; PHC = photocoagulation; PMA = postmenstrual age; ROP = retinopathy of prematmity; SD = standard deviation; wks = weeks.
[a]Fisher exact test.
[b]*t* test.
[c]Mann–Whitney *U* test.

recurrence of fibrovascular tissue is almost impossible. The follow-up period after vitrectomy exceeded 6 months in all eyes in the analysis. All surgeries were performed by 1 surgeon (N.A.).

Data collected from each case record included gender, gestational age, birth weight, the Apgar score at 5 minutes, the duration of intubation, and the presence of severe systemic complications (i.e., hydrocephalus, patent ductus arteriosus, or necrotizing enterocolitis requiring surgery). We included the duration of intubation as an indicator of the degree of oxygen exposure. ROP findings included the preoperative ROP stage, zone, fibrovascular tissue and vitreous base adhesion, clock hours of fibrovascular tissue, postmenstrual age at the initial application of photocoagulation, photocoagulation to both vascularized and nonvascularized retina (Figure 1) or only to nonvascularized retina (Figure 2), postmenstrual age at vitrectomy, and intraoperative hemorrhage. Although the area of photocoagulation generally is limited to the nonvascularized retina, because the importance of photocoagulation to the vascularized retina has been suggested in eyes with severe ROP,[15,16] we included eyes treated with photocoagulation applied to both the vascularized and nonvascularized retina. ROP findings were recorded by detailed retinal drawings and RetCam (Massie Research Laboratories, Inc, Pleasanton, California, USA). The eyes that fulfilled the inclusion criteria were divided into 2 groups based on the recurrence or absence of recurrence of fibrovascular tissue after surgery. The factors listed previously were compared between the 2 groups.

Statistical analyses were performed using statistical software (StatLab, SPSS for Windows, version 16.0; SPSS, Inc, Chicago, Illinois, USA). Univariate analyses to determine the association between risk factors and recurrence after early vitrectomy were performed using the Mann–Whitney *U* test, the *t* test, and the Fisher exact test as appropriate. A multivariate logistic regression model was constructed with recurrence as the dependent variable and with the factors that differed at the significance level of $P < .2$ in univariate analyses, including the gestational age, preoperative ROP stage, fibrovascular tissue and vitreous base adhesion, the postmenstrual age at the initial application of photocoagulation, and photocoagulation to both the vascularized and nonvascularized retina as independent variables. $P < .01$ was considered significant.

RESULTS

A TOTAL OF 50 EYES OF 31 PATIENTS (19 GIRLS, 12 BOYS) underwent early vitrectomy. Among them, 5 (10%) eyes that had not received sufficient photocoagulation even to the nonvascularized retina and 2 (4%) eyes that had extensive fibrovascular tissue adhesion to the vitreous base were excluded. Forty-three eyes (86%) of 29 patients were included. Of the 29 patients, 19 were girls and 10 were boys, with a mean gestational age of 25.2 ± 2.3 weeks and a mean follow-up of 23.8 ± 10.7 months.

Eight (18.0%) of 43 eyes had a recurrence of fibrovascular tissue after surgery (Figure 2), and the others did not have a recurrence and the retina reattached (Figure 1). The recurrences, which began 2 to 8 weeks after surgery and progressed gradually, were characterized by proliferation that developed mainly toward the vascularized posterior retina probably via the residual vitreous framework, where fibrous strands often formed between the disc and the fibrovascular tissue with an irregular tractional retinal detachment (Figure 2). Three of the 8 eyes underwent a second vitrectomy 1 to 2 months after surgery because of severe recurrent fibrovascular tissue with a total retinal detachment. Because recurrent fibrovascular tissue adhered strongly to the retina where the tissue was not removed completely, retinal reattachment was obtained in only 1 eye. Four of 8 eyes had a recurrence of fibrovascular tissue that was less severe with a partial retinal attachment after primary surgery, and 1 eye had early progression to phthisis bulbi, and a second vitrectomy was not performed.

The data and statistics are summarized in the Table. There were more boys in the recurrence group than in the nonrecurrence group, but the difference was not significant ($P = .042$). There were no significant differences in the other baseline characteristics between the 2 groups. Before surgery, the incidences of both stage 4B and fibrovascular tissue adhesion to the vitreous base were slightly higher in the recurrence group, but these did not reach significance ($P = .067$ and $P = .037$, respectively). Photocoagulation was applied more often to both vascularized and nonvascularized retina in the group in which there was no recurrence of fibrovascular tissue compared with the group in which there was recurrence (74.3% vs 12.5%); the difference between the two was significant ($P = .002$). There was no difference in the ROP findings between the 2 groups. Multivariate analyses using a stepwise logistic regression model also showed that only photocoagulation to both the vascularized and nonvascularized retina (odds ratio, 0.049; 95% confidence interval, 0.005 to 0.459; $P = .008$) was associated with postoperative recurrence of fibrovascular tissue, and the other factors were not significantly associated with recurrence.

DISCUSSION

THE RECURRENT FIBROVASCULAR TISSUE DEVELOPED mainly toward the posterior retina in 8 eyes. The main purpose of early vitrectomy to treat AP ROP is to remove the vitreous framework through which fibrovascular tissue aggressively and rapidly grows to reach the posterior lens surface and the ciliary body or vitreous base, which has condensed vitreous.[9] Thus, almost all vitreous gel, especially in the vitreous base and around the fibrovascular tissue, needs to be resected during vitrectomy; however, some vitreous gel remains on the surface of the posterior retina because of tight adherence to the retina[17] that prevents creation of a posterior vitreous detachment. In addition, vitreous on the avascular retina that is anterior to the fibrovascular tissue is liquefied partially by dense photocoagulation,[18] in contrast to vitreous on the vascularized posterior retina. Consequently, recurrent fibrovascular tissue can develop easily on the posterior retina via the residual vitreous when the disease activity is not controlled before surgery.

Three of 8 eyes with recurrent fibrovascular tissue underwent a second vitrectomy. Because vitreous attachment to the retina in neonates is very strong where the dense collagen fibers of the vitreous are connected to the retina,[17] tight adhesion develops between the recurring fibrovascular tissue and the retina. Thus, once the tissue forms, total removal of the tissue to release the traction is almost impossible, and attention must be paid to developing prophylactic measures to prevent recurrence of the fibrovascular tissue.

Although early vitreous surgery prevents progression of retinal detachment and dramatically improves the visual prognosis of AP ROP,[9] the current study showed that some eyes had postoperative recurrence of fibrovascular tissue and that photocoagulation applied to vascularized retina may be the most important factor to minimize the incidence of recurrence. In classic ROP, the retinal vasculature is completed in the vascularized posterior retina,[19] where photocoagulation to only nonvascularized retina is sufficient.[2] In contrast, a wide-field area of hypoperfusion has been detected in nonvascularized retina and in vascularized retina in AP ROP.[20] In these cases, application of photocoagulation to only the nonvascularized retina is insufficient, because angiogenic factor continues to be released from the hypoperfusion retina[21,22] that is already vascularized, although angiogenic factor in the vitreous cavity may be washed out transiently by vitrectomy.[23]

One report on eyes with AP ROP suggested the importance of additional application of photocoagulation to the nonvascularized retina beneath regressing flat neovascularization that is left untreated,[24] and several studies reported the necessity of applying photocoagulation to already vascularized retina posterior to the junction.[15,16] Our previous study[20] and the results of the current study strongly suggested that dense photocoagulation to both the

vascularized retina and nonvascularized retina in eyes with AP ROP is essential for a good prognosis because it prevents aggressive disease progression and inhibits postoperative recurrence of fibrovascular proliferation. However, extensively applied photocoagulation not only to nonvascularized retina but also to vascularized retina may have several side effects, including reduced night vision, insufficient dark adaptation, loss of peripheral vision, blind spots, a risk of cystoid macular edema, and neovascularization. However, preserving the posterior retina by extensive preoperative photocoagulation and early vitreous surgery may be more beneficial for visual prognosis in patients with AP ROP.

Although an anti-vascular endothelial growth factor drug that inhibits the process of neovascularization prevents progression of the severe form of ROP,[25–27] the drug also causes excessive scar formation in ROP.[26,28] A transforming growth factor beta antagonist and rho kinase inhibitor are candidates for preventing vitreoretinal proliferation.[29] A preoperative or postoperative enzymatic approach for vitreolysis may reduce recurrence by resolving the residual vitreous gel that is difficult to detach from the retina mechanically;[30] however, the effects of such drugs on ROP have not been studied, and the long-term systemic effects on neonates are unknown. In addition, because the activity of AP ROP is very high, their contribution to the treatment of AP ROP may be minimal. Meanwhile, photocoagulation to treat ROP is safe. Thus, preoperative photocoagulation that includes the vascularized posterior retina may be the most reasonable approach for obtaining good visual prognosis in eyes with AP ROP.

The limitations of the current study are its retrospective nature, the absence of a control group, and the nonstandardized protocols for both photocoagulation and vitrectomy in patients with AP ROP in some institutions. Nevertheless, the total sample size of 50 eyes and the follow-up periods ranging from 7 to 42 months seem adequate for analyzing a correlation between recurrence after early vitreous surgery and the associated risk factors. A randomized controlled trial is warranted.

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