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Neovascularization From Scleral Wound as Cause of Vitreous Rebleeding After Vitrectomy for Proliferative Diabetic Retinopathy

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Purpose: To determine the site of rebleeding into the vitreous after vitrectomy in patients with diabetic retinopathy.

Methods: We studied in detail 4 eyes of 4 patients in whom rebleeding into the vitreous followed successful vitrectomy for proliferative diabetic retinopathy. In addition, the fibrous membrane removed at surgery was studied by light and electron microscopy.

Results: In these 4 eyes, the second operation revealed that the source of the vitreous rebleeding was from a fibrovascular proliferation around the scleral wounds of the initial surgery, and no other neovascularization and/or reproliferation were observed in the whole retina. Rebleeding in these 4 eyes developed at an average of 9 weeks after initial surgery. The proliferative membrane was oval in shape and expanded from the residual vitreous that had been incarcerated in the scleral wound. The proliferative membrane removed during vitrectomy was poor in cellular components and contained extracellular matrix. Blood vessels of various sizes were also present. Electron microscopy showed the membrane was rich in extracellular components and contained high and low electron density cells. These cells often had microvilli and seemed to be of epithelial origin.

Conclusions: These findings show that vitreous rebleeding may develop from fibrovascular proliferation from the scleral wound created during initial surgery. The proliferated membrane showed histological similarities with the fibrovascular proliferation usually seen in the diabetic retina and may represent a type of anterior proliferation secondary to retinal ischemia. **Jpn J Ophthalmol 2000;44:154–160**

Key Words: Neovascularization from scleral wound, proliferative diabetic retinopathy, retinal ischemia, vitrectomy.

Introduction

Vitreous rebleeding after pars plana vitrectomy for proliferative diabetic retinopathy has been attributed to incomplete membrane dissection, incomplete hemostasis by endodiathermy, or fibrovascular reproliferation in the posterior pole of the retina. The fibrovascular proliferation that occurs around the scleral wound after the initial surgery has also been suggested as a contributory cause of vitreous rebleeding several weeks after surgery.[1–4] However, few studies have examined the effect of this proliferative membrane in detail.

In this study, we present 4 cases in which fibrovascular proliferation around the scleral wound is believed to have been the source of the vitreous rebleeding after the initial surgery. We discuss the clinical and morphological characteristics of these proliferative membranes.

Materials and Methods

Between February and November 1994, the authors performed pars plana vitrectomy for diabetic retinopathy on 120 eyes. In 11 of these eyes, vitreous

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Table 1. Clinical Data of 4 Eyes With Fibrovascular Membrane at Scleral Wound

Patient No. Age/Sex	Preoperative Fundus Exam	Lens	Duration of reVH after First Operation (wk)	Methods of Second Operation	Range of Proliferative Membrane*	Treatment of Proliferative Membrane	Postoperative Complications	Visual Acuity	
								Preop	Postop
1/47/F	VH + NVG	Phakic	3	PPV + PPL	++	Complete excision	NVG + VH	20/400	30 cm/mm
2/62/M	MTRD + NVG	Phakic	12	PPV + PEA	+++	Partial excision	VH	20/600	10/600
3/52/F	MTRD	Phakic	9	PPV + PPL + IOL	+	Partial excision	VH	20/400	10/400
4/74/M	EMTRD + VH	IOL	12	PPV	++	Diathermy	None	20/400	20/200

VH: vitreous hemorrhage, NVG: neovascular glaucoma, MTRD: macular tractional retinal detachment, EMTRD: extramacular tractional retinal detachment, PPV: pars plana vitrectomy, PPL: pars plana lensectomy, PEA: phacoemulsification aspiration, IOL: intraocular lens.

+: Limited around wound, ++: spread but not crossed ora serrata, +++: spread and crossed ora serrata.

rebeleeding occurred after initial surgery. We examined 4 eyes (4 patients) of these 11 eyes. Two of the 4 patients were men, and 2 were women. Their ages ranged from 47 to 74 years (mean age = 58.89 years).

Before the first operation, all 4 eyes had active proliferative diabetic retinopathy with fibrovascular proliferative membranes. In 2 eyes, macular tractional retinal detachment had occurred. One eye had vitreous hemorrhage accompanied by an extramacular tractional retinal detachment. The fibrovascular membranes were limited to the optic disc in one eye, extended from the optic disc to the vascular arcade in 2 eyes, and extended from the posterior pole to the nasal quadrants in 1 eye. Three eyes were phakic and one was pseudophakic. Two of the phakic eyes exhibited rubeosis iridis before initial surgery, and neovascular glaucoma was also present. In all 4 eyes, only partial retinal photocoagulation had been performed before the first operation.

The first vitrectomy was performed as follows: after much of the vitreous gel had been removed, vitreous scissors were used to segment and delaminate the fibrovascular membrane in the posterior pole. After panretinal endophotocoagulation, fluid-air exchange was performed in 2 eyes. The crystalline lenses in the 3 aphakic eyes and the intraocular lens in the 1 pseudophakic eye were all preserved and no severe complications were observed during any of the operations.

Despite the presumed success of the initial surgery, vitreous rebleeding occurred 4–12 weeks (mean = 9.0 ± 4.6 weeks) later. As there was no absorption of vitreous rebleeding, reoperations were performed 5–19 weeks (mean = 10.8 weeks) after the first vitrectomy. Reoperations were performed as follows. Lensectomies were performed in all 3 phakic eyes and the intraocular lens removed from the pseudophakic eye. To remove the residual vitreous, we performed vitreous shaving by scleral indentation. During this procedure, close examination of the peripheral retina, ora serrata, pars plana, and ciliary body revealed that the fibrovascular membranes appeared to be the source of the vitreous rebleeding, and that these were present only in the scleral wounds of the initial surgery. A second surgery on these 4 eyes revealed that the source of the vitreous rebleeding was the fibrovascular proliferation around the scleral wouunds, and no other neovascularization and/or reproliferation were observed in the whole retina. These membranes were removed by using horizontal vitreous scissors and/or endodiathermy coagulation in all cases. In 1 case, the fibrovascular membrane could be extracted in one piece during membrane delamination. It was fixed in 0.1 M phosphate buffer containing 2.5% glutaraldehyde for 24 hours. This specimen was then prepared for light and electron microscopy.

Results

The preoperative conditions, surgical methods, and postoperative courses of the 4 patients are summarized in Table 1. In all cases, the proliferative membranes, which were observed during surgery at the sites of the scleral wounds, extended radially from a base in the residual vitreous that had become incarcerated in the scleral wounds created during the initial surgery. The proliferative membranes were oval in shape and stretched as a membrane toward the residual vitreous surrounding the wound. The

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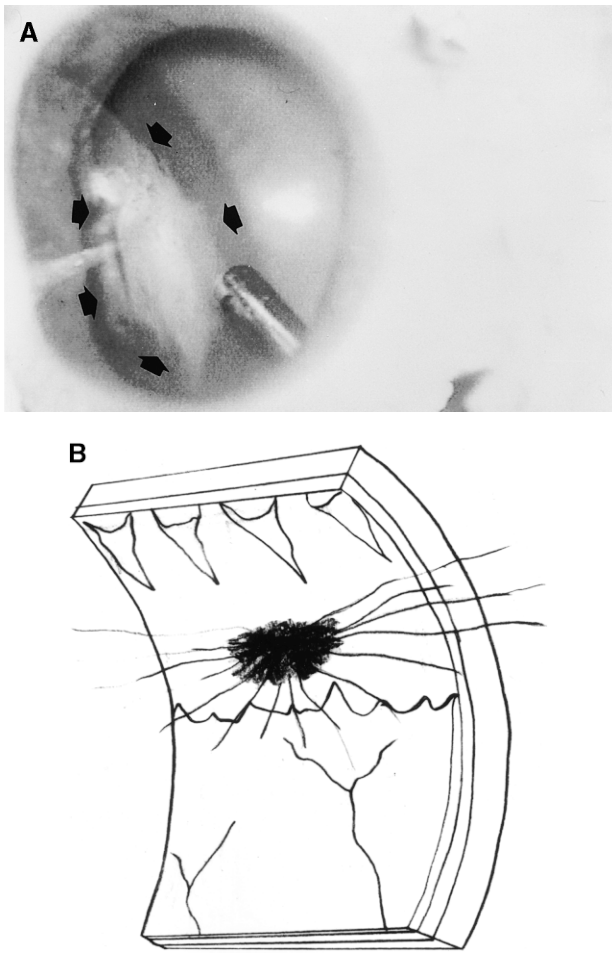

Figure 1. (**A**). Case 1. Neovascularization at scleral wound from initial vitrectomy spread to peripheral retina but did not reach ora serrata. Field shown was observed directly under surgical microscope during scleral indentation (arrows: proliferative membrane). (**B**) Case 1. Schematic diagram of proliferative membrane that did not reach ora serrata. Drawing also shows ciliary body, ora serrata, and peripheral retina. Proliferative membrane spread radially with the incarcerated residual vitreous created at initial surgery as origin. Oval-shaped membrane extends in membranous form toward circumference.

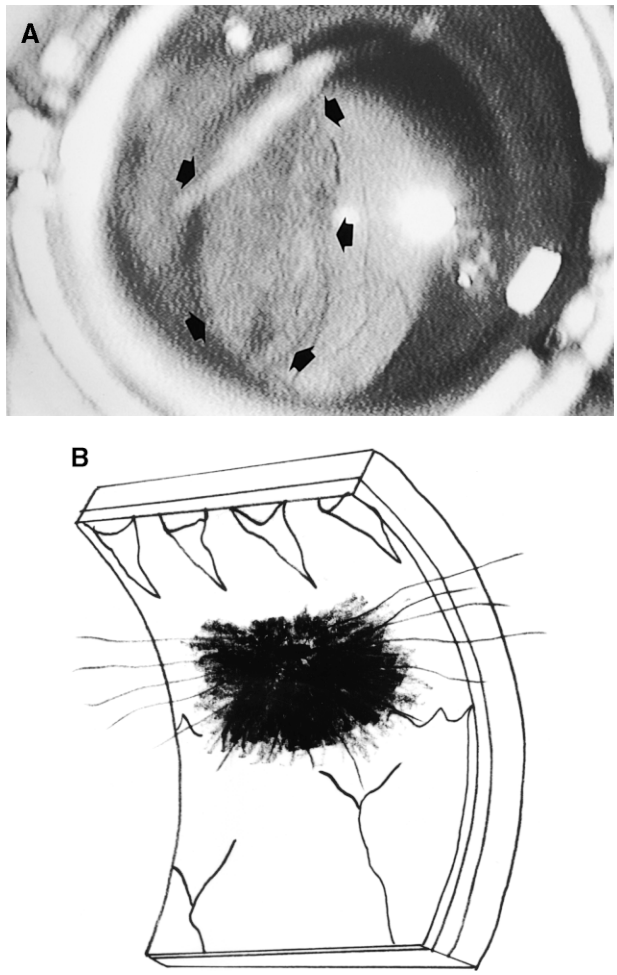

Figure 2. (**A**) Case 2. Case in which proliferative membrane crossed ora serrata and reached peripheral retina. Photograph shows field observed directly under surgical microscope during scleral indentation. Ora serrata is not visible in posterior part of proliferative membrane (arrows). (**B**) Case 2. Schematic diagram of Figure 2A. Proliferative membrane has expanded further than seen in Figure 1B, crossing ora serrata and forming broad proliferative membrane that reaches peripheral retina. Proliferative membrane extends radially along residual vitreous with scleral wound as origin.

proliferative membrane was localized in the periphery of the scleral wound in 1 eye, was spread around the scleral wound but did not cross the ora serrata in 2 eyes, and crossed the ora serrata and reached the peripheral retina in 1 eye.

The proliferative membranes contained large amounts of vascular components and were almost the same color as fibrovascular membranes ordinarily seen in the posterior pole in proliferative diabetic retinopathy. In all 4 patients, neovascularization was present in the upper 2 o'clock and 10 o'clock positions, and in the lower infero-temporal scleral wounds. These were the positions that were used to insert the surgical instruments during the initial vitrectomy. The main origin of vitreous rebleeding was thought to be the 2 o'clock wound in 2 eyes, and the 10 o'clock wound in the other 2 eyes.

Figure 1A shows the field observed directly under the surgical microscope when scleral indentation was performed in case 1. The ora serrata is visible in the posterior pole of the proliferative membrane. Figure 1B is a schematic drawing of the proliferating mem-

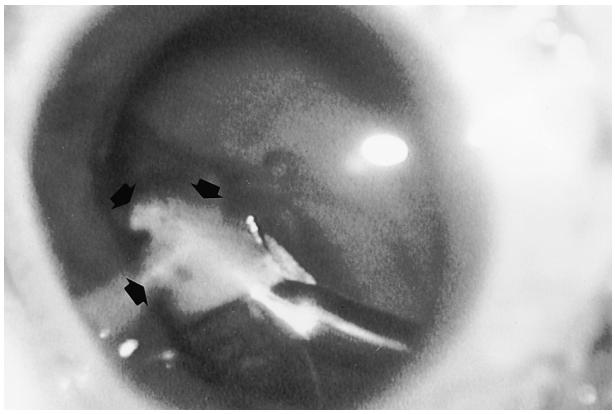

Figure 3. Case 1. Adherent portion of proliferative membrane (arrows) at scleral wound was delaminated by use of horizontal vitreous scissors.

brane and shows the ciliary body, ora serrata, and peripheral retina. Figure 2A shows the field observed under the surgical microscope when scleral indentation was performed in case 2. The membrane reached the peripheral retina but the ora serrata was not visible. The color tone in this case was somewhat reddish because of the rich neovascularization in the proliferative membrane. Figure 2B is a schematic drawing of the existing morphology of the proliferative membrane in case 2.

Membrane delamination, using a horizontal vitreous scissors, was performed to treat the proliferative membrane in case 1 (Figure 3). In this case, the adhering parts of the membrane were delaminated and the membrane could be extracted in one piece using

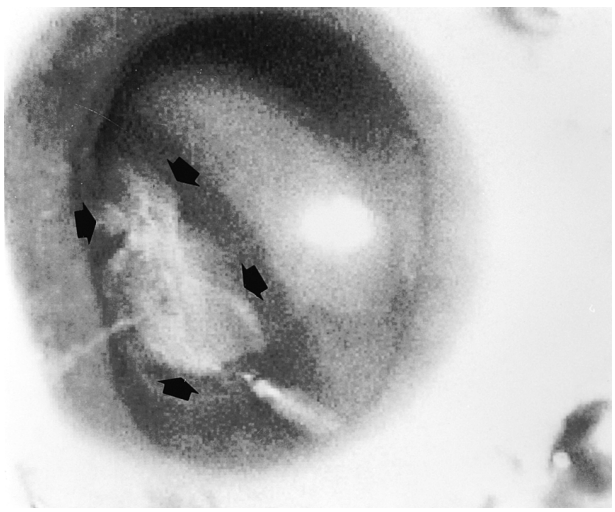

Figure 4. Case 3. Endodiathermy was performed to coagulate proliferative membrane (arrows).

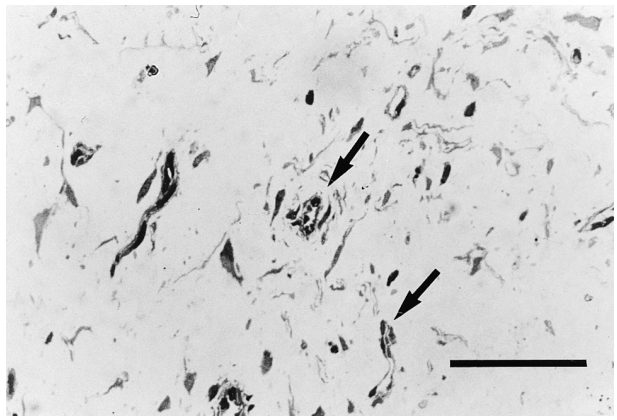

Figure 5. Light microscopic findings of proliferative membrane. Main components of membrane are extracellular matrix and fibroblasts. Blood vessels with various luminal diameters are visible in scattered locations (arrows). Bar = 50 μm.

delamination technique. However, in cases 2 and 3, only partial extraction of the membrane was possible, after which tissue coagulation was performed by endodiathermy. In case 4, hemostasis was achieved only by endodiathermic coagulation. Bleeding occurred during membrane treatment, however hemostasis was achieved by endodiathermy in all cases (Figure 4).

Postoperatively, neovascular glaucoma developed in 1 eye and vitreous rebleeding occurred in 3 eyes. Additional panretinal photocoagulation in all cases and transscleral cyclophotocoagulation in 1 case were then performed. Despite the additional treatment, intraocular pressure was uncontrollable in case 2. Improvement in visual acuity of two lines or more was obtained in 1 eye, no change was observed in 1 eye, and the visual acuity worsened by two lines or more in the other 2 eyes. The follow-up period ranged between 24 and 27 months (mean = 25.3 months).

Histopathological examination of the proliferative membrane excised in one piece from case 1 was performed. Light microscopy revealed that the membrane contained a large amount of extracellular matrix, a few cells and occasional blood vessels with various luminal diameters (Figure 5). Electron microscopy revealed that the large extracellular component consisted of two kinds of cells, those with high and those with low electron densities, dispersed over a wide area. Most of the two kinds of cells had microvilli (Figure 6A). Some of the cells with microvilli and lumen-like morphology appeared to be immature endothelial cells (Figure 6B). In addition, macrophages containing a large number of pigment

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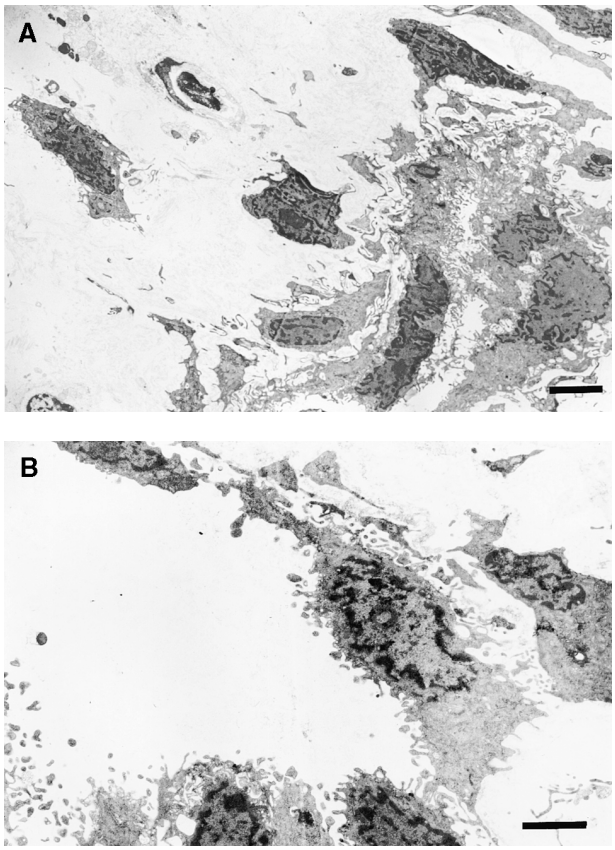

Figure 6. (**A**) Electron microscopy of proliferative membrane (case 1). Large quantities of extracellular matrix are present, and large numbers of high or low electron density cells are scattered over a wide area. Most cells of both cell types have microvilli. Bar = 3 μm. (**B**) Some cells with microvilli and lumen-like form seem to be immature endothelial cells. Bar = 2 μm.

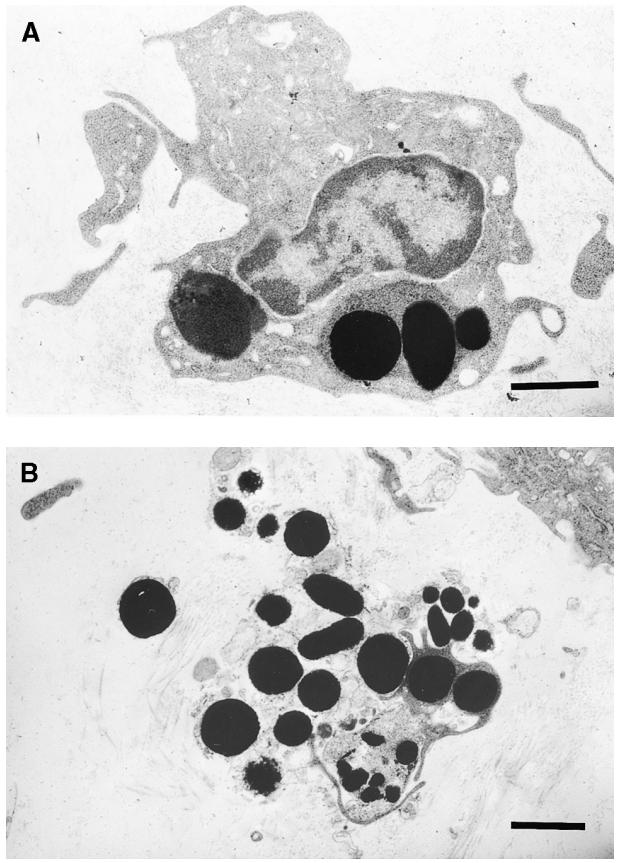

Figure 7. (**A**) Macrophages containing many pigmented granules were also observed in proliferative membrane of case 1. Bar = 1 μm. (**B**) Melanocyte-like degenerative cells containing large numbers of granules were also seen in delaminated membrane. Bar = 1 μm.

granules (Figure 7A) and melanocyte-like degenerative cells containing a large number of granules were also observed (Figure 7B).

Discussion

Vitreous rebleeding that occurs several weeks after primary vitrectomy has been attributed to fibrovascular reproliferation both from the posterior pole of the eye and from the scleral wound resulting from the initial operation.[1,2] Proliferative tissue in the scleral wound after pars plana vitrectomy was first reported in 1977 by Tardif and Schepens.[2] In 1987, Lewis and coworkers[5,6] reported the existence of proliferative changes that grow along the anterior vitreous, starting from the peripheral retina, thus giving rise to "anterior hyaloid fibrovascular proliferation" (AHFVP). Neovascularization at the scleral wound was reported by us in 46% of patients with vitreous rebleeding after initial vitrectomy. This anterior proliferative tissue is believed to be the result of proliferative changes caused by retinal ischemia and it arises along the anterior residual vitreous.

The AHFVP reported by Lewis and colleagues[5,6] had postoperative complications, including vitreous hemorrhage, peripheral tractional retinal detachment, and hypotony caused by fibrovascular membranes that arose in the peripheral retina after the initial vitrectomy for active proliferative diabetic retinopathy. However, this type of proliferative tissue is seldom seen. Most cases in which anterior proliferative changes occur after initial diabetic vitrectomy are believed to involve fibrovascular membranes arising from the scleral wound.[1–4] We performed fundus examination using binocular indirect ophthalmoscopy combined with scleral indentation and observed the gradual development of white fibrovascular membranes beginning about 3–4 weeks after

the initial surgery. These membranes continued to grow for about 2 months. Such fibrovascular membrane growth is especially marked in cases that exhibit highly active proliferative diabetic retinopathy before surgery.

Previous studies have demonstrated that the proliferative membrane usually observed in the posterior pole of the retina in patients with proliferative diabetic retinopathy, consists of various kinds of cells, including macrophages, fibroblasts, glial cells, and vascular endothelial cells, as well as extracellular matrix such as collagen.[7–10] These proliferative membranes differ from those seen in proliferative vitreoretinopathy by the dominant contribution of retinal pigmentary epithelial cells.[11,12] Also, membranes in the former contain vascular components.[13–16] The proliferative membranes removed in the present study contained large quantities of extracellular matrix, a few cellular components and scattered blood vessels with various luminal diameters. These features, as well as the pathological findings, are similar to those of proliferative membranes derived from proliferative diabetic retinopathy. However, the proliferative membranes removed in the present study contained large quantities of cells with microvilli. The neovascularization that occurs in proliferative diabetic retinopathy arises from the retinal vein. In contrast, the proliferative membranes in the scleral wounds are believed to be fibrovascular proliferation of a different origin. Some cells in the proliferative membranes at a scleral wound are accompanied by melanin, probably from the ciliary epithelial cells, because the ciliary epithelial cells at the scleral wound proliferate after initial vitrectomy.[17]

In the present study, tractional retinal detachment was caused by highly active fibrovascular proliferative membranes before the initial surgery in 3 eyes. In all cases, panretinal photocoagulation was not completed before initial surgery. In cases 1 and 2, neovascular glaucoma was a preoperative complication. During the initial surgery, cutting of the peripheral vitreous was performed to the greatest possible extent in all 4 eyes. However, because the lens was preserved in the 3 phakic eyes, vitreous removal in the peripheral posterior chamber was incomplete. The proliferative membrane grew along the residual vitreous, and total removal of the anterior vitreous by lensectomy at the second operation may have stopped vitreous rebleeding in these 4 cases.

Although the neovascularization at the scleral wound reported in the present study is a different pathological condition from the AHFVP reported by Lewis and associates,[5,6] both conditions result from a high degree of retinal ischemia, and both exhibit anterior proliferative changes along the peripheral residual vitreous. Because of the localization in the eye, the proliferative tissue must be removed by lensectomy in all cases. Furthermore, angiogenesis factors, such as vascular endothelial growth factor[18] derived from ischemic retina, can easily reach the anterior vitreous part and induce proliferative changes. This would then increase the risk of postoperative neovascular glaucoma.[19] However, there is the possibility that these anterior proliferative changes also exaggerate the anterior ischemia and induce neovascular glaucoma. Thorough panretinal photocoagulation combined with lensectomy and complete retinal reattachment appear to be essential at the initial vitrectomy for proliferative diabetic retinopathy patients.

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