Jpn J Ophthalmol (2015) 59:236–243
DOI 10.1007/s10384-015-0382-4

THE OFFICIAL INTERNATIONAL JOURNAL OF THE JAPANESE OPHTHALMOLOGICAL SOCIETY

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CLINICAL INVESTIGATION

Macular morphologic findings on optical coherence tomography after microincision vitrectomy for proliferative diabetic retinopathy

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Received: 24 October 2014 / Accepted: 6 April 2015 / Published online: 9 May 2015

Abstract

Purpose To investigate macular morphology on spectral-domain optical coherence tomography (SD-OCT) images after microincision vitrectomy for vitreous hemorrhage associated with proliferative diabetic retinopathy (PDR).

Methods In this retrospective case series, 69 eyes (57 consecutive patients) that underwent 23-gauge microincision vitrectomy for vitreous hemorrhage due to PDR were investigated. Qualitative and quantitative characteristics on SD-OCT images [central retinal thickness, external limiting membrane (ELM), and the ellipsoid zone, epiretinal membranes involving the fovea, and hyperreflective foci at the fovea] were assessed 6 months postoperatively. Their association with the logarithm of the minimum angle of resolution visual acuity (logMAR VA) was evaluated.

Results The ELM was disrupted in 15 and the ellipsoid zone in 27 eyes, and associated significantly ($P < 0.001$, for both comparisons) with poor visual outcomes 6 months postoperatively. Hyperreflective foci in the outer retinal layers were associated with either a disrupted ELM or ellipsoid zone and poor prognoses ($P < 0.001$, for all comparisons). The accumulation of hyperreflective foci at the fovea in five eyes was correlated significantly ($P < 0.001$) with poorer logMAR VA. Twenty-nine eyes had center-involved diabetic macular edema 6 months postoperatively, whereas the central thickness was not correlated with the logMAR VA ($R = -0.148$, $P = 0.224$). Eight eyes with either epiretinal membrane on SD-OCT images had greater central thickness ($P = 0.003$), although there were no differences in the logMAR VA between eyes with and without it ($P = 0.648$).

Conclusions Foveal photoreceptor damage is associated with poor visual outcomes after microincision vitrectomy for vitreous hemorrhage due to PDR.

Keywords Hyperreflective foci · Microincision vitrectomy surgery · Optical coherence tomography · Photoreceptor · Proliferative diabetic retinopathy

Introduction

Diabetic retinopathy (DR) is a leading cause of decreased visual acuity (VA) in patients of working age. Neovascular complications in proliferative diabetic retinopathy (PDR), i.e., vitreous hemorrhage, tractional retinal detachment, and rubeotic glaucoma in particular, often result in severe visual impairment [1, 2]. Diabetes induces loss of the retinal capillary beds, where ischemia or hypoxia increase the expression of vascular endothelial growth factor (VEGF) [3, 4]. Concomitantly, neovascularization at the vitreoretinal interface, in association with fibrous proliferation, exacerbates contraction of the posterior vitreous cortex, leading to vitreous hemorrhage and tractional retinal detachment.

Panretinal photocoagulation, the gold standard treatment for PDR, decreases the demand for oxygen and nutrients in the retinal tissue and increases the intraocular concentration of oxygen [5–7]. Vitrectomy also has been performed to treat neovascular complications due to PDR including vitreous hemorrhage, tractional retinal detachment, and traction maculopathy, either alone or combined with anti-VEGF therapy [8–13]. Vitrectomy dramatically improves the visual prognosis in patients with PDR, although

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surgeons have been concerned about the intraoperative and postoperative complications associated with 20-gauge vitrectomy [14–16]. Microincision vitrectomy surgery (MIVS), a major advance in this field [17–19], reduces the risks of iatrogenic retinal tears and simplifies removal of the proliferative tissues in PDR [20, 21]. Concomitantly, complications affecting the visual prognosis occur less frequently, although what determines the visual outcomes after MIVS for PDR is still poorly understood. In addition, the vitreous hemorrhage makes it impossible to find the preoperative prognostic factors on OCT images, which often confuses clinicians because of poor visual outcomes despite successful surgery.

Improved optical coherence tomography (OCT) technology has enabled evaluation of the macular morphologic changes in diabetic macular edema (DME) [22–24]. Originally, time-domain OCT quantified the macular thickness, which is modestly correlated with the VA [25]. Higher resolution images on spectral-domain (SD) OCT provide better delineation of the fine physiological and pathological structures. The ellipsoid zone of the photoreceptors, which had been previously regarded as the junction between inner and outer segments, is depicted as the highly reflective band on SD-OCT images [26]. The ellipsoid zone contains accumulated mitochondria and supports the metabolism of photoreceptor cells, and it is clinically reported to have a better association with the VA in ME associated with retinal vascular diseases [27]. The external limiting membrane (ELM) on SD-OCT images is another marker of photoreceptor integrity at the fovea [24, 28]. SD-OCT also delineates solitary or accumulated higher reflective dots, called hyperreflective foci, in diabetic retinas, which is believed to correspond to the precursor of hard exudates or lipid-laden macrophages [29]. Clinically, hyperreflective foci are related to foveal photoreceptor damage and concomitant visual disturbances [30, 31]. Whereas these findings have been well characterized in DME, macular lesions on OCT images in eyes with PDR remain ill defined.

It is a clinical concern that vitreous hemorrhage due to PDR does not allow us to know the preoperative retinal status and to predict visual prognoses in eyes with vitreous hemorrhage due to PDR that underwent MIVS, although macular lesions are expected to have great impact on visual function. We thus evaluated the qualitative and quantitative parameters of macular morphologies on SD-OCT images and their association with visual disturbance after the surgery.

Subjects and methods

Patients

We retrospectively reviewed 69 eyes of 57 patients (age range 24–80 years; mean 60.1 ± 11.1 years) who underwent 23-gauge MIVS for vitreous hemorrhage due to PDR with more than 6 months of follow-up at the Department of Ophthalmology of Kyoto University Hospital from April 2009 to October 2012. The inclusion criteria were persistent vitreous hemorrhage over more than a few months or several recurrent episodes of vitreous hemorrhage that reduced the baseline VA and the availability of SD-OCT images of sufficient quality at 6 months postoperatively. The major exclusion criteria were the presence of neovascular glaucoma and other ocular diseases affecting visual dysfunction except for cataracts, eyes in which tractional retinal detachment at the macula was observed preoperatively or intraoperatively, eyes with recurrent or persistent vitreous hemorrhages at 6 months, eyes that underwent additional surgery, and eyes in which the surgery was combined with silicon oil tamponade. All research and measurements adhered to the tenets of the Declaration of Helsinki. The ethics committee of our institution approved the study protocol.

Interventions

After inducing local anesthesia with sub-Tenon's injection of 2 % xylocaine, we performed cataract surgery (phacoemulsification and aspiration) in 59 eyes with cataracts. We then inserted a 23-gauge cannula and performed core vitrectomy as described previously [32], with the removal of proliferative tissues or the epiretinal membrane (ERM) if present. The residual vitreous in the periphery was shaved, and the retinas in the periphery were photocoagulated with an endolaser. Intraoperative oozing or bleeding from the retinal vasculature or neovascularization was coagulated by diathermy. Sulfur hexafluoride (SF_6) gas was injected to tamponade the bleeding or retinal tears in five eyes. Thirty-five eyes with either severe PDR or more endolaser shots were treated with a sub-Tenon's injection of triamcinolone (20 mg) at the end of surgery. We performed additional retinal photocoagulation postoperatively in 28 eyes.

Optical coherence tomography

Retinal sectional images of the macula were acquired using SD-OCT (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) with infrared images [24]. The retinal thickness at the central 1-mm subfield on the Early Treatment Diabetic Retinopathy Study (ETDRS) grid was measured on the OCT maps constructed by raster scans (30 × 25 degrees) as described previously [24]. We evaluated the status of the ellipsoid zone and ELM and the presence of ERM on 30-degree cross-hair images centered on the fovea [33]. The presence of hyperreflective foci in the outer retinal layers at the fovea were determined to be hyperreflective foci in the areas outside of the (presumed) ELM [31]. The accumulation of hyperreflective foci at the fovea was defined as the presence of confluent hyperreflective foci on the foveal retinal pigment epithelium (RPE), which corresponded to the hard exudates on the color fundus photographs.

Statistical analysis

The results are expressed as the mean ± standard deviation. Either the Student's *t* test or analysis of variance was used to compare the quantitative data populations with normal distributions and equal variance. The data were analyzed using the Mann-Whitney *U* test for populations with non-normal distributions or unequal variance. Linear regression analysis (with Bonferroni correction if necessary) was performed to test the statistical correlation. The differences in sampling distribution were evaluated using the chi-square test. $P < 0.05$ was considered statistically significant.

Results

Pre- and intraoperative characteristics

We first evaluated the prognostic factors after MIVS but failed to find significant associations of the logMAR VA at 6 months with either preoperative factors or intraoperative procedures (Table 1). ERM and proliferative tissues involving the fovea were intraoperatively diagnosed in 25 eyes and peeled during the surgery. Such eyes had greater central thickness at 6 months than those without intraoperative ERM (340 ± 65 vs. 304 ± 58 μm; $P = 0.018$), although there were no differences in visual outcomes between them (0.391 ± 0.426 vs. 0.264 ± 0.348; $P = 0.183$). No other factors were associated with the central retinal thickness.

Optical coherence tomographic characteristics 6 months postoperatively

To explain the visual disturbances after MIVS, we investigated the characteristics on SD-OCT images postoperatively. Twenty-nine eyes had center-involved DME, although there was no association between the central thickness and logMAR VA at 6 months ($R = -0.148$, $P = 0.224$) (Fig. 1; Table 2). Although we removed ERM diagnosed intraoperatively in 25 eyes, ERM was seen in 8 eyes 6 months after the surgery that was not correlated with the logMAR (Table 2). However, the accumulated hyperreflective foci at the fovea corresponding to foveal hard exudates were significantly correlated ($P < 0.001$) with poor visual outcomes (Table 2).

Compared to these parameters, which could be diagnosed by fundus biomicroscopy to some extent, SD-OCT specifically delineated the photoreceptor markers and hyperreflective foci. We found that 42 eyes with intact ellipsoid zone lines had significantly better visual outcomes at 6 months than those with either a discontinuous or absent ellipsoid zone (Fig. 2; Table 2). An intact ELM line at the fovea was also significantly associated with better logMAR at 6 months (Table 2). Collectively, foveal photoreceptor damage was related to poor visual outcomes postoperatively, as in the case of treatment-naïve DME [28, 34–36]. Hyperreflective foci in the outer retinal layers were identified in 24 eyes, which had significantly ($P < 0.001$) poorer visual outcomes than those without them (Table 2).

Table 1 Pre- and intraoperative characteristics and their correlation with LogMAR VA or central thickness 6 months after MIVS for vitreous hemorrhage due to PDR

Parameter		Association with logMAR VA at 6 months	Association with central thickness at 6 months
Age (years)	60.1 ± 11.1	$R = 0.061$, $P = 0.617$	$R = -0.181$, $P = 0.137$
Hemoglobin A1c (%)	7.10 ± 1.52	$R = -0.135$, $P = 0.305$	$R = 0.204$, $P = 0.117$
Hypertension	40	$P = 0.797$	$P = 0.186$
Hyperlipidemia	27	$P = 0.543$	$P = 0.301$
Baseline logMAR VA	1.477 ± 0.537	$R = 0.146$, $P = 0.230$	$R = -0.186$, $P = 0.125$
Baseline iris or angle neovascularization	4 eyes	$P = 0.083$	$P = 0.091$
Combined with cataract surgery	59 eyes	$P = 0.973$	$P = 0.461$
Combined with sub-Tenon's injection of triamcinolone	36 eyes	$P = 0.744$	$P = 0.372$

logMAR VA logarithm of the minimal angle of resolution visual acuity

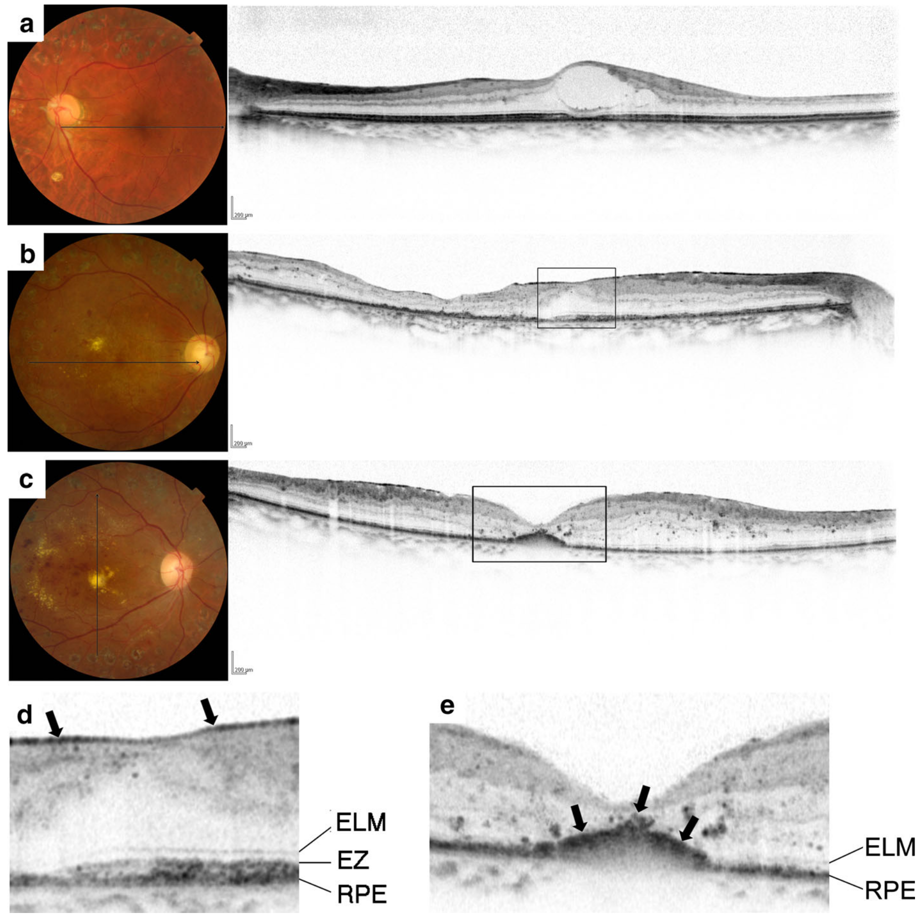

Fig. 1 Fundus photographs and optical coherence tomography images. **a** Representative cases with refractory macular edema, **b** epiretinal membrane (ERM), and **c** accumulation of hyperreflective foci at the fovea corresponding to hard exudates 6 months after microincision vitrectomy surgery for proliferative diabetic retinopathy. **d** The magnified image shows ERM involving the fovea (*arrow*). **e** The external limiting membrane (ELM) and the ellipsoid zone (EZ) are disrupted around the confluent hyperreflective foci (*arrows*) on the retinal pigment epithelium (RPE) in the magnified image

Photoreceptor damage and other findings

We found a significant ($P < 0.001$) association between the status of the ellipsoid zone and ELM (Table 3), as shown in DME [37]. Most eyes (88.9 %) without hyperreflective foci in the outer retinal layers had an intact ellipsoid zone, whereas either a discontinuous or absent ellipsoid zone was found in most eyes (91.7 %) with the foci ($P < 0.001$) (Table 3). The ellipsoid zone line was absent in all eyes with accumulated hyperreflective foci compared to those without the foci ($P < 0.001$). Neither the central retinal thickness nor the presence of ERM was associated with the status of the ellipsoid zone (Table 3).

Eyes with ERM or accumulated hyperreflective foci had greater central retinal thickness than those without such findings ($P < 0.003$ and $P = 0.039$, respectively) (Table 4). However, we did not find an association between the central thickness and the status of ELM line or the presence of hyperreflective foci in the outer retinal layers (Table 4).

Discussion

Media opacity does not allow us to predict visual outcomes using OCT findings, which often leads to uncertainty by surgeons following a successful MIVS for vitreous hemorrhage due to PDR. Indeed, we did not identify preoperative factors predictive of the visual outcomes in this study, although several ocular and systemic prognostic factors have been reported [38–41]. We did show for the first time the clinical relevance of a disrupted ellipsoid zone or ELM on SD-OCT images after MIVS for vitreous hemorrhage due to PDR, suggesting the potential utility of SD-OCT examination after surgery. The incidence of these OCT findings was lower than in eyes with DME reported in the previous publications [31], which might help clinicians to predict the visual prognoses to some extent. In addition, central thickness was not associated with visual impairment in these eyes, compared to the modest correlation between them in treatment-naïve DME, although we could not determine the necessity of additional treatment for postoperative DME. Despite the dramatic efficacy of the

Table 2 Association between visual outcomes and characteristics on SD-OCT images 6 months after MIVS for vitreous hemorrhage due to PDR

Parameter	logMAR VA at 6 months	Association with logMAR VA at 6 months
Central thickness	0.310 ± 0.380	$R = -0.148$, $P = 0.224$
ERM		
Present (8 eyes)	0.303 ± 0.384	$P = 0.648$
Absent (61 eyes)	0.369 ± 0.368	
Accumulated hyperreflective foci		
Present (5 eyes)	0.996 ± 0.243	$P < 0.001$
Absent (64 eyes)	0.256 ± 0.335	
Ellipsoid zone		
Intact (42 eyes)	0.105 ± 0.155	$P < 0.001$
Discontinuous (16 eyes)	0.380 ± 0.281*	
Absent (11 eyes)	0.995 ± 0.253*†	
ELM		
Intact (54 eyes)	0.145 ± 0.194	$P < 0.001$
Discontinuous (5 eyes)	0.730 ± 0.199*	
Absent (10 eyes)	0.995 ± 0.269*	
Hyperreflective foci in the outer retinal layers		
Present (24 eyes)	0.626 ± 0.426	$P < 0.001$
Absent (45 eyes)	0.142 ± 0.213	

ELM external limiting membrane, *ERM* epiretinal membrane, *logMAR VA* logarithm of the minimal angle of resolution visual acuity

* $P < 0.01$ vs. intact

† $P < 0.01$ vs. discontinuous

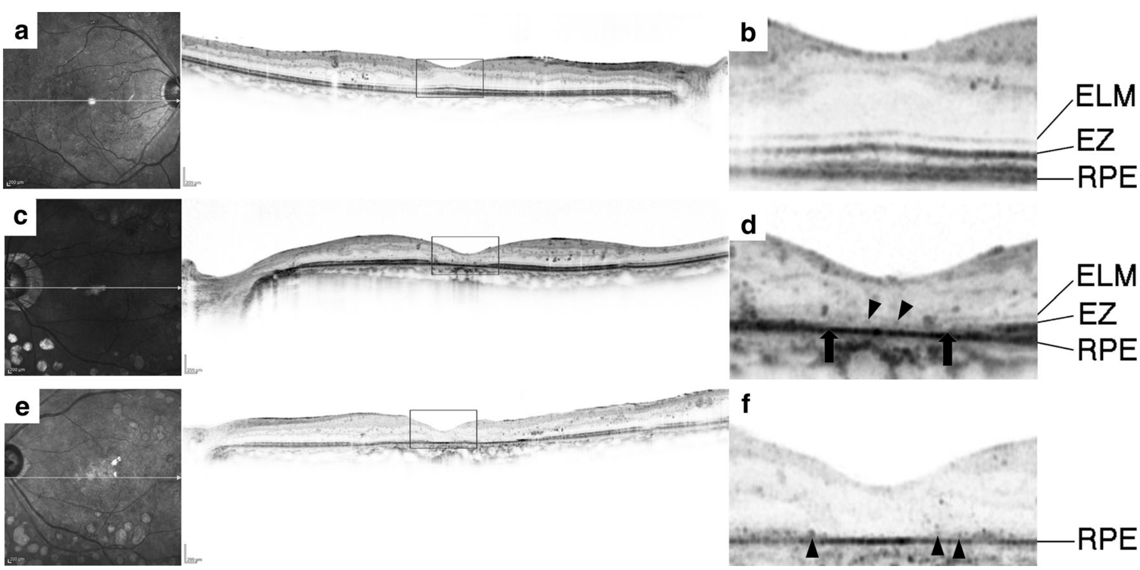

Fig. 2 Representative cases with various patterns of foveal photoreceptor damage 6 months after microincision vitrectomy surgery for proliferative diabetic retinopathy. **a, b** Both the external limiting membrane (ELM) and the ellipsoid zone (EZ) are intact. The best-corrected decimal VA is 1.2. **c, d** The ELM is discontinuous, and the EZ is absent between the *arrows*. The best-corrected VA is 0.3. The *arrowheads* indicate hyperreflective foci in the outer retinal layers. **e, f** The ELM and EZ are absent at the fovea, whereas the hyperreflective foci are delineated in the outer layers (*arrowheads*). The best-corrected VA is 0.15

Table 3 Association of the ellipsoid zone and other OCT characteristics after MIVS for vitreous hemorrhage due to PDR

Parameter	Intact ellipsoid zone	Discontinuous ellipsoid zone	Absent ellipsoid zone	*P* value
ELM				
Intact	42	12	0	<0.001
Discontinuous	0	4	1	
Absent	0	0	10	
Hyperreflective foci in the outer retinal layers				
Present	2	11	11	<0.001
Absent	40	5	0	
Accumulated hyperreflective foci				
Present	0	0	5	<0.001
Absent	42	16	6	
Central thickness (μm)	320 ± 58	314 ± 62	312 ± 87	0.903
ERM				
Present	4	2	2	0.721
Absent	38	14	9	

ELM external limiting membrane, *ERM* epiretinal membrane

Table 4 Relationship between central retinal thickness and other parameters on OCT images after MIVS for vitreous hemorrhage due to PDR

Parameter	Central thickness (μm)	*P* value
ERM		
Present	378 ± 75	0.003
Absent	309 ± 57	
Accumulated hyperreflective foci		
Present	373 ± 95	0.039
Absent	313 ± 59	
ELM		
Intact	322 ± 58	0.243
Discontinuous	272 ± 25	
Absent	316 ± 90	
Hyperreflective foci in the outer retinal layers		
Present	310 ± 76	0.473
Absent	321 ± 55	

ELM external limiting membrane, *ERM* epiretinal membrane

procedure, surgeons have often encountered severe intra- and postoperative complications, which influence prognoses in eyes treated with 20-gauge vitrectomy for PDR [14–16, 42]. Taken together, clinicians should systematically consider the prognostic factors including complications and macular morphological findings.

Clinicians had explained that traction maculopathy, ischemic maculopathy, or macular degeneration make the visual outcomes poorer in eyes after successful vitrectomy for PDR [43]. SD-OCT clearly showed a disrupted ellipsoid zone, and less frequently the disrupted ELM line represents the photoreceptor damage more directly [28, 37]. The current study showed that the changes in these lines were associated significantly with visual outcomes after MIVS performed to treat vitreous hemorrhage due to PDR, although another possible parameter to evaluate the photoreceptor damage might be the thickness of the outer nuclear layer. In addition, subfoveal hard exudates in the color photographs corresponded to the accumulated hyperreflective foci on SD-OCT images [29, 30], associated with poorer prognosis. In contrast, we did not objectively evaluate macular ischemia using SD-OCT, although a previous study reported a subjective finding, thinning of the ganglion cell layers in ischemic maculopathy [44]. We evaluated another prognostic factor, optic nerve atrophy, but failed to find the differences in visual outcomes between eyes with and without it ($P = 0.103$), and further functional and structural analyses should be planned as in other optic nerve diseases [45].

Despite the clinical relevance of the ELM and ellipsoid zone on SD-OCT images, the mechanisms of the photoreceptor degeneration after MIVS for PDR are largely unknown. Epidemiologic publications report that DME often occurs in eyes with PDR [2], suggesting that photoreceptor damage in this study depends on the pathogenesis of DME, which might be represented to some extent by retinal thickening and hyperreflective foci. However, we did not find an association between the central thickness and photoreceptor damage. These data prompted several considerations. It is reported that vitrectomy was effective for DME [46, 47], which resolved after MIVS for PDR. Previous DME might lead to photoreceptor disturbance in some eyes. The subfoveal accumulation of hyperreflective foci is reported to result from absorption of subretinal fluids containing hyperreflective foci, which would contribute to photoreceptor damage [30]. Another explanation is the phototoxicity by surgery with a longer time for severe fibrovascular proliferation [48].

In the current study, 29 eyes had center-involved DME 6 months postoperatively, although we did not find a significant association between the central retinal thickness and VA after MIVS in eyes with vitreous hemorrhage due to PDR. It is widely accepted that the foveal thickness is correlated modestly with visual impairment in treatment-naïve DME [25]. This discrepancy suggests the efficacy of vitrectomy for DME in these case series, because it is also reported that the association was not evident postoperatively and that the VA changes paradoxically after interventions for DME [25, 32]. Eyes with ERM had greater central retinal thickness, suggesting that the ERM contributes to macular thickening [49]. Although these parameters were not associated with the VA, we have to consider preventive strategies for residual DME or postoperative ERM, such as inner limiting membrane peeling, and to evaluate the efficacy of individual treatments for DME refractory to vitrectomy.

Although the current study was small and retrospective, we recommend evaluation of the qualitative and quantitative parameters of the macular morphologies after MIVS for vitreous hemorrhage due to PDR.

Conflicts of interest T. Murakami, None; A. Uji, None; K. Ogino, None; N. Unoki, None; S. Yoshitake, None, Y. Dodo, None; T. Horii, None, K. Nishijima, None; N. Yoshimura; None.

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