



Treatment of macular hemorrhage in retinal arterial microaneurysm: anatomic site-oriented therapy

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Abstract

Purpose To investigate the usefulness of anatomic site-oriented therapy for macular hemorrhage secondary to retinal arterial macroaneurysm (RAM).

Study design Retrospective observational study, clinical case series

Methods Twenty-seven consecutive patients (27 eyes) with macular hemorrhage secondary to RAM were classified according to the retinal layer(s) with hemorrhage identified by optical coherence tomography into 4 types and treated differentially. Vitrectomy was conducted for subinternal limiting membrane hemorrhage (SILMH), intravitreal gas injection for subretinal hemorrhage (SRH) or intraretinal hemorrhage (IRH), and vitrectomy and intravitreal air/gas exchange for multilevel hemorrhage (at least 2 among SILMH/SRH/IRH).

Results Complete displacement or resolution of the macular hemorrhage was achieved in all 27 eyes: 7 with SILMH, 7 with SRH, 3 with IRH, and 10 with multilevel hemorrhage. Compared with the baseline score, the 3-month postoperative Early Treatment Diabetic Retinopathy Study score (mean \pm SD) improved significantly in SILMH ($+42.9 \pm 6.9$ letters; $P < .0001$, paired t test), multilevel hemorrhage ($+23.9 \pm 14.4$ letters; $P = .0005$), and SRH ($+17.7 \pm 18.4$ letters; $P = .0440$), but not in IRH ($+6.7 \pm 9.0$ letters; $P = .3228$). Compared with the baseline thickness, the 3-month postoperative central retinal thickness decreased significantly in multilevel hemorrhage ($-930.3 \pm 290.8 \mu\text{m}$; $P < .0001$), SILMH ($-628.4 \pm 177.0 \mu\text{m}$; $P < .0001$), IRH ($-508.3 \pm 72.1 \mu\text{m}$; $P = .0066$), and SRH ($-476.9 \pm 300.0 \mu\text{m}$; $P = .0056$). The central ellipsoid zone was detectable in 7/7 eyes with SILMH but in none of the eyes in the other 3 groups ($P < .0001$). No retinal detachment or macular hole occurred in any eyes.

Conclusion For macular hemorrhage secondary to RAM, anatomic site-oriented therapy using different treatments targeting the hemorrhagic retinal layers is useful. The optimal treatments for individual hemorrhagic retinal layers require further studies.

Keywords Anatomic site-oriented therapy · Macular hemorrhage · Mixed hemorrhage · Optical coherence tomography · Retinal macroaneurysm

Introduction

Representative diseases that cause macular hemorrhage include age-related macular degeneration (AMD), polypoidal choroidal vasculopathy (PCV), and retinal arterial macroaneurysm (RAM). Both “vitrectomizing techniques” [1–9]

and “nonvitrectomizing techniques” [10–19] are available for the treatment of macular hemorrhage, both resulting in visual improvement. A review of 38 studies on vitrectomizing and nonvitrectomizing treatments for (sub)macular hemorrhage secondary to AMD found no difference in the rate of complete displacement, recurrent (sub)macular hemorrhage, or vitreous hemorrhage between the 2 treatments [20]. However, treatment outcomes have not been adequately studied for RAM, because there are only few reports on “vitrectomizing techniques” [4, 8, 9] and “nonvitrectomizing techniques” [13, 15] for 2 or more eyes. Moreover, most of the reports in the literature investigated treatment of submacular hemorrhage, and few studies

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examined strategies targeting hemorrhages at various anatomic sites, including multilayer hemorrhage.

Recurrence of macular hemorrhage differs depending on the etiology. For AMD, macular hemorrhage that has resolved with treatment has been reported to recur in 20% of the cases at 9.1 months after treatment [3], in 20% of the cases at 6 months [12], and in 41% of the cases at 18.4 months [15]. For AMD and PCV, long-term follow-up and intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) are required to prevent recurrence [3, 12, 15, 19]. For RAM, recurrence is rare if the macular hemorrhage is resolved and the RAM subsides with or without treatment [4, 8, 13, 15].

Macular hemorrhage may occur in different layers of the retina. For AMD and PCV, subretinal hemorrhage is the main type, and the photoreceptor and outer nuclear layers become damaged from the early stage [21–24]. The mean visual acuity in patients after 2 years of developing macular hemorrhage deteriorates to 20/1250, showing the need for prompt treatment [25]. For RAM, hemorrhage may occur in any of the retinal layers: subinternal limiting membrane hemorrhage, subretinal hemorrhage, intraretinal hemorrhage, and multilevel hemorrhage. Damage to the retinal photoreceptor cells thus differs depending on the site of hemorrhage. As a result, the visual outcome after treatment presumably varies.

The treatment for macular hemorrhage depends on the etiology. Intravitreal recombinant tissue plasminogen activator (rt-PA) is accepted as an efficient treatment for macular hemorrhage in AMD. In contrast, intravitreal injection of rt-PA in eyes with RAM carries a risk of causing vitreous hemorrhage [15]. For this reason, if RAM is detected, photocoagulation has to be performed before intravitreal injection of rt-PA.

As mentioned above, macular hemorrhage secondary to RAM can occur in any of the retinal layers, which presumably affects the visual outcome. This kind of disorder cannot be treated with a uniform therapy. Instead, treatment for macular hemorrhage should target the anatomic site of hemorrhage while considering the timing of photocoagulation for RAM. With recent improvement in the resolution of optical coherence tomography (OCT), the location of macular hemorrhage secondary to RAM can be identified clearly. In the present study, we examined the usefulness of the strategy of anatomic site-oriented therapy for macular hemorrhage secondary to RAM, by conducting differential treatments targeting the hemorrhagic retinal layers observed on OCT.

Patients and methods

Inclusion and exclusion criteria

The present retrospective study was performed by reviewing the medical records obtained from November 2013 through

September 2017 at the Department of Ophthalmology of Nihon University Hospital. This study was approved by the ethics committee of the Nihon University School of Medicine (approved on October 13, 2016; no. 161001). All the patients gave written informed consent to undergo treatment after receiving full explanations of the procedure and of its potential merits and risks.

The inclusion criteria were thick macular hemorrhage caused by RAM, which involved the foveal center and measured at least 1 disc diameter, and treatment conducted less than 8 weeks from symptom onset. The exclusion criteria were causes of macular hemorrhage other than RAM and presence of macular diseases such as epiretinal membrane in the fellow eye.

RAM was diagnosed from the findings of fundus photography, OCT (Spectralis; Heidelberg Engineering), and indocyanine angiography. According to the hemorrhagic retinal layer observed on OCT, macular hemorrhage was classified into (1) subinternal limiting membrane hemorrhage, (2) intraretinal hemorrhage, and (3) subretinal hemorrhage. A combination of two or more of (1), (2), and (3) was classified as multilevel hemorrhage.

Gas injection with/without TPA

Eyes with subretinal hemorrhage or intraretinal hemorrhage were treated with 1 session of intravitreal injection of perfluoropropane (C_3F_8 ; Alcon Laboratories,) with or without rt-PA (Alteplase; Kyowa Hakko Kirin) performed in an outpatient room. When RAM was diagnosed before treatment, photocoagulation was conducted first, followed by intravitreal injection of gas and rt-PA. When RAM was not diagnosed before treatment, intravitreal injection of gas to displace the hemorrhage was conducted first, followed by photocoagulation.

All the intravitreal injections were conducted by 1 ophthalmologist (Y.K.). After retrobulbar block using 4 mL of 2% xylocaine was performed, the eyelid skin was disinfected with 10% povidone-iodine (Meiji Seika), and the conjunctiva, with 0.25% povidone-iodine diluted in physiological saline [26]. Then the eye was draped, and a lid speculum was placed. After paracentesis (0.3 mL) was performed, perfluoropropane (C_3F_8 ; 0.3 mL) with or without rt-PA (25 μ A/0.05 mL, 40,000 IU) was injected intravitreally through the pars plana. The patient was placed in a sitting position for 2 h. Thereafter, the patient was admitted and then maintained in a prone position for 2 days.

Vitrectomy

Eyes with subinternal limiting membrane hemorrhage or multilevel hemorrhage were treated with vitrectomy. Vitrectomy was performed using the Constellation system (Alcon

Laboratories). Under retrobulbar anesthesia, 25-G vitrectomy was performed at a cut rate of 5000 per minute (cpm) and linear aspiration of 0 to 650 mmHg. For posterior visualization, the RESIGHT 700 (Carl Zeiss Meditec) was used. After core vitrectomy, internal limiting membrane peeling was performed using 25-G or 27-G internal limiting membrane forceps (Alcon Laboratories) and a plano-concave contact lens (Hoya). After removing the subinternal limiting membrane hemorrhage, retinal photocoagulation was performed on the macroaneurysm. Then fluid, air, or gas (17% sulfur hexafluoride or 9% perfluoropropane) exchange was conducted. Patients who had subretinal hemorrhage were placed in a prone position for 2 days after the fluid, air, or gas exchange.

Simultaneous cataract surgery was conducted in patients aged 50 years or older because cataract tends to progress after vitrectomy. Cataract surgery was conducted using either of the following 2 types of viscoelastic materials: Viscoat (Alcon Laboratories) or Healon (AMO). Phacoemulsification (Constellation) was performed through an incision in the superior cornea. A foldable intraocular lens (SN60WF, Alcon Laboratories or iSert Micro 255, Hoya Corporation) was inserted inside the capsule.

Preoperative and postoperative examinations

The patients were examined before, 1 to 2 days, 1 week, 2 weeks, 1 month, 2 months, and 3 months after the surgery. All underwent Snellen best-corrected visual acuity (BCVA) testing, Early Treatment Diabetic Retinopathy Study (ETDRS) scoring, intraocular pressure measurement, slit-lamp biomicroscopy, indirect ophthalmoscopy, and OCT before and at 1, 2, and 3 months after the surgery. The greatest diameter of subretinal hemorrhage was measured and expressed in disc diameters (vertical disc diameter = 1 disc diameter). Displacement or resolution of the macular hemorrhage was evaluated by use of fundus photography 1 week after the surgery. Complete displacement or resolution was defined as no blood or only a scanty amount of blood within 1 disc diameter of the foveal center [19]. Recurrence of the lesion was diagnosed by evaluating rebleeding by use of color fundus photography and by measuring the central retinal thickness (CRT) on OCT. The presence or absence of the central ellipsoid zone at the foveal center was observed on OCT and graded as undetectable or detectable. The fellow eye was measured by OCT and used for comparison as the unaffected eye.

Statistical analysis

Statistical analyses were performed using SPSS software version 21 (SPSS). Data were expressed as medians (range), means \pm standard deviations (SD), and

percentages. The Kruskal-Wallis test was used to compare the data of the 4 groups. When the Kruskal-Wallis test detected a significant difference, the Steel-Dwass test was conducted as the post hoc test to compare 2 groups. The paired *t* test or Mann-Whitney test was used to compare data between 2 groups. Probability values less than .05 were considered significant.

Results

Baseline data

We studied 27 eyes of 27 patients (20 women) with a median age of 76 (range, 55–87) years. The median interval between the onset of symptoms and surgery was 12 (range, 1–51) days. The median greatest diameter of the macular hemorrhage was 3.2 (range, 1.5–7.5) disc diameters. The median pretreatment Snellen BCVA in the affected eye was 20/222 (range, 20/1000–20/25), and the median ETDRS score was 34 (range, 6–79) letters. The median CRT in the affected eyes was 823 (range, 354–1549) μ m, and that in the unaffected fellow eyes, 203 (range, 155–289) μ m.

Subinternal limiting membrane hemorrhage was found in 7 eyes; subretinal hemorrhage, in 7 eyes; intraretinal hemorrhage, in 3 eyes; and multilevel hemorrhage, in 10 eyes (Table 1). Among the eyes with multilevel hemorrhage, 8 eyes had subinternal limiting membrane hemorrhage + subretinal hemorrhage, and 2 eyes had subinternal limiting membrane hemorrhage + intraretinal hemorrhage. No significant difference in age was found among the 4 groups ($P = .2136$, Kruskal-Wallis test). The interval from onset to treatment differed significantly among the 4 groups ($P = .0266$). However, no significant difference was found between the multilevel hemorrhage group and the other 3 groups ($P = .3881$ vs subretinal hemorrhage, $P = .2979$ vs intraretinal hemorrhage, and $P > .9999$ vs subinternal limiting membrane hemorrhage; Kruskal-Wallis test followed by Steel-Dwass test). The size of the macular hemorrhage differed significantly among the 4 groups ($P = .0046$). The relationships between the multilevel hemorrhage group and the other 3 groups were as follows: $P = .0056$ vs subinternal limiting membrane hemorrhage, $P = .0673$ vs subretinal hemorrhage, and $P = .0673$ vs intraretinal hemorrhage. The preoperative ETDRS score did not differ significantly among the 4 groups ($P = .3386$). The preoperative CRT did differ significantly among the 4 groups ($P = .0077$). The relationships between the multilevel hemorrhage group and the other 3 groups were as follows: $P = .0077$ vs subretinal hemorrhage, $P = .1690$ vs intraretinal hemorrhage, and $P = .5268$ vs subinternal limiting membrane hemorrhage.

Table 1 Characteristics of the 4 groups, treatments, and parameters before and after anatomic site-oriented therapy

Parameter		SILM hemorrhage (n = 7)	SR hemorrhage (n = 7)	IR hemorrhage (n = 3)	Multilevel hemorrhage (n = 10)	P value	
Median age, y (range)		74 (67–85)	77 (55–82)	84 (80–87)	76 (57–85)	.2136 ^a	
Median duration of macular hemorrhage, d (range)		14 (7–51)	7 (3–15)	3 (1–5)	17 (4–50)	.0266 ^a	
Median size of macular hemorrhage, DD (range)		2.5 (1.5–3.8)	3.2 (2.6–3.9)	2.8 (2.1–3.1)	4.6 (2.8–7.5)	.0046 ^a	
Treatment		PEA+ IOL + VIT + air/gas	C ₃ F ₈ IVI ± rt-PA	C ₃ F ₈ IVI	*PEA + IOL + VIT ± air/gas		
ETDRS, letters	Median preop, (range)	41 (22–48)	31 (8–79)	34 (29–61)	29 (6–46)	.3386 ^a	
	Mean ± SD	37.7 ± 8.7	37.3 ± 24.3	41.3 ± 17.2	26.8 ± 11.7		
	Median postop, 3 mo (range)	80 (77–85)	50 (35–80)	50 (35–59)	54 (27–78)		.0039 ^a
	Mean ± SD	80.6 ± 3.9	55.0 ± 15.7	48.0 ± 12.1	50.7 ± 17.0		
CRT, μm	Median change (range)	44 (34–55)	12 (1–50)	6 (–2–16)	22 (3–52)	.0065 ^a	
	Mean ± SD	+42.9 ± 6.9	+17.7 ± 18.4	+6.7 ± 9.0	+23.9 ± 14.4		
	P value ^b (preop vs postop)	< .0001	.0440	.3288	.0005		
	P value ^c (postop vs unaffected eye)	.0639	.0017	.8273	.0191		
Central ellipsoid zone, D/U	Median preop,(range)	823 (665–1218)	456 (354–1223)	650 (637–774)	1044 (661–1549)	.0077 ^a	
	Mean ± SD	886.7 ± 197.5	592.7 ± 301.5	687.0 ± 75.6	1072.9 ± 267.7		
	Median postop, 3 mo (range)	259 (163–318)	110 (101–153)	185 (151–200)	101 (55–394)		.0054 ^a
	Mean ± SD	258.3 ± 52.6	115.9 ± 18.5	178.7 ± 25.1	142.6 ± 101.6		
Central ellipsoid zone, D/U	Median change (range)	–569 (–417 to 959)	–354 (–242 to 1096)	–486 (–450 to 589)	–962 (–466 to 1368)	.0237 ^a	
	Mean ± SD	–628.4 ± 177.0	–476.9 ± 300.0	–508.3 ± 72.1	–930.3 ± 290.8		
	P value ^b (preop vs postop)	< .0001	.0056	.0066	< .0001		
	P value ^c (postop vs unaffected eye)	.0639	.0017	.8273	.0191		
Central ellipsoid zone, D/U	Preop	2/7	0/7	0/3	0/10	.1036 ^d	
	Postop	7/7	0/7	0/3	0/10		< .0001 ^d

SILM subinternal limiting membrane, SR subretinal, IR intraretinal, *Multilevel* at least 2 among SILM, SR, and IR hemorrhage, DD disc diameter, ETDRS Early Treatment Diabetic Retinopathy Study, CRT central retinal thickness, D/U detectable/undetectable, Preop preoperative, Postop postoperative, PEA phacoemulsification, IOL intraocular lens, VIT vitrectomy, rt-PA recombinant tissue plasminogen activator, C₃F₈, perfluoropropane, IVI intravitreal injection

*PEA + IOL not done in 1 case

^aKruskal-Wallis test

^bPaired *t* test

^cMann-Whitney test

^dChi-square test

Primary outcome measure

At 3 months posttreatment, the mean ETDRS score had increased significantly from the baseline score in eyes with subinternal limiting membrane hemorrhage ($P < .0001$, paired *t* test; change in ETDRS score from baseline [Δ ETDRS score]: $+42.9 \pm 6.9$ letters), in eyes with subretinal hemorrhage ($P = .0440$; Δ ETDRS score: $+17.7 \pm 18.4$ letters), and in eyes with multilevel hemorrhage ($P = .0005$;

Δ ETDRS score: $+23.9 \pm 14.4$ letters), but did not differ significantly in eyes with intraretinal hemorrhage ($P = .3288$; Δ ETDRS score: $+6.7 \pm 9.0$ letters; Table 1). The change in the ETDRS score at 3 months posttreatment was better in the subinternal limiting membrane hemorrhage group than in the other 3 groups ($P = .0093$ vs intraretinal hemorrhage, $P = .0217$ vs subretinal hemorrhage, and $P = .0759$ vs multilevel hemorrhage; Kruskal-Wallis test followed by Steel-Dwass test).

At 3 months posttreatment, the mean CRT had decreased significantly from that at baseline in eyes with subinternal limiting membrane hemorrhage ($P < .0001$, paired t test; change in CRT from baseline [Δ CRT]: $-628.4 \pm 177.0 \mu\text{m}$), subretinal hemorrhage ($P = .0056$; Δ CRT: $-476.9 \pm 300.0 \mu\text{m}$), intraretinal hemorrhage ($P = .0066$; Δ CRT: $-508.3 \pm 72.1 \mu\text{m}$), and multilevel hemorrhage ($P < .0001$; Δ CRT: $-930.3 \pm 290.8 \mu\text{m}$), showing significant improvement in all 4 groups. However, the CRT at 3 months posttreatment was significantly thinner in eyes with subretinal hemorrhage (median [range]: 110 [101–153] μm ; $P = .0017$, Mann-Whitney test) and in eyes with multilevel hemorrhage (101 [55–394] μm ; $P = .0191$) than in unaffected fellow eyes (203 [155–289] μm).

Representative cases of subinternal limiting membrane hemorrhage (Fig. 1), subretinal hemorrhage (Fig. 2),

intraretinal hemorrhage (Fig. 3), and multilevel hemorrhage (Fig. 4) are presented.

Secondary outcome measures

Complete macular hemorrhage displacement or resolution was achieved in all 27 eyes (100%). At 3 months after surgery, the central ellipsoid zone was detected in 7 of the 7 eyes with subinternal limiting hemorrhage, but in none of the eyes in the other 3 groups ($P < .0001$; Table 1). Regarding postoperative complications, no retinal detachment or macular hole formation was observed, whilst mild vitreous bleeding occurred in 2 eyes, and intraretinal hemorrhage recurred in 1 eye. The mild vitreous bleeding and intraretinal hemorrhage were resorbed spontaneously (Table 2).

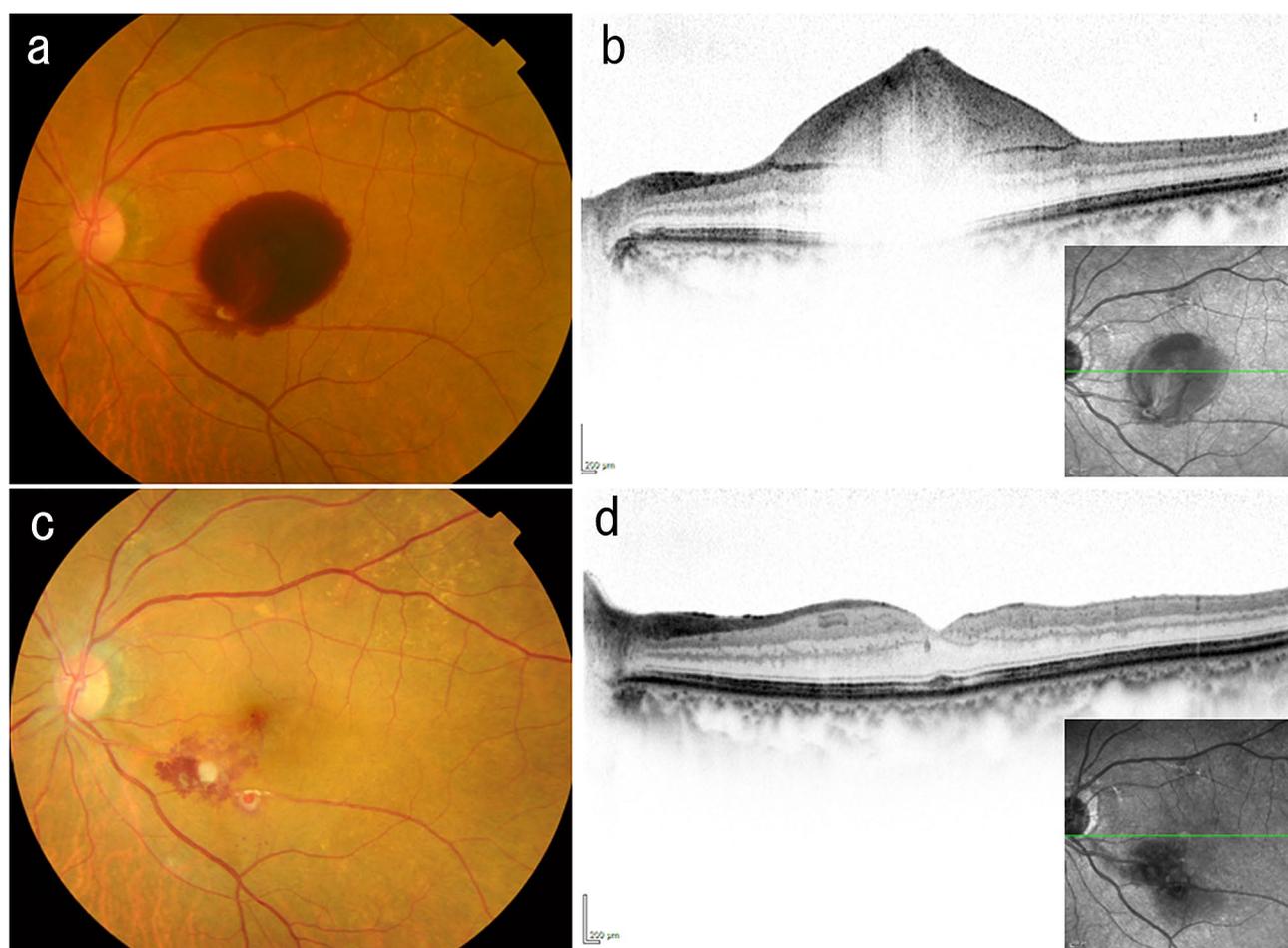


Fig. 1 Preoperative and postoperative findings of a case of subinternal limiting membrane hemorrhage. **a** Before surgery, a hemorrhage measuring 2.6 disc diameters and involving the fovea was observed. The Early Treatment Diabetic Retinopathy Study (ETDRS) score was 41. **b** The preoperative central retinal thickness (CRT) measured on optical coherence tomography was 823 μm . **c** The retinal hemorrhage

was removed by cataract surgery + vitrectomy + fluid air exchange. A mild subretinal hemorrhage was observed; hence, fluid-air exchange was performed. The 3-month postoperative ETDRS score was 85. Photocoagulation was not performed. **d** The 3-month postoperative CRT was 236 μm , and the central ellipsoid zone was detectable

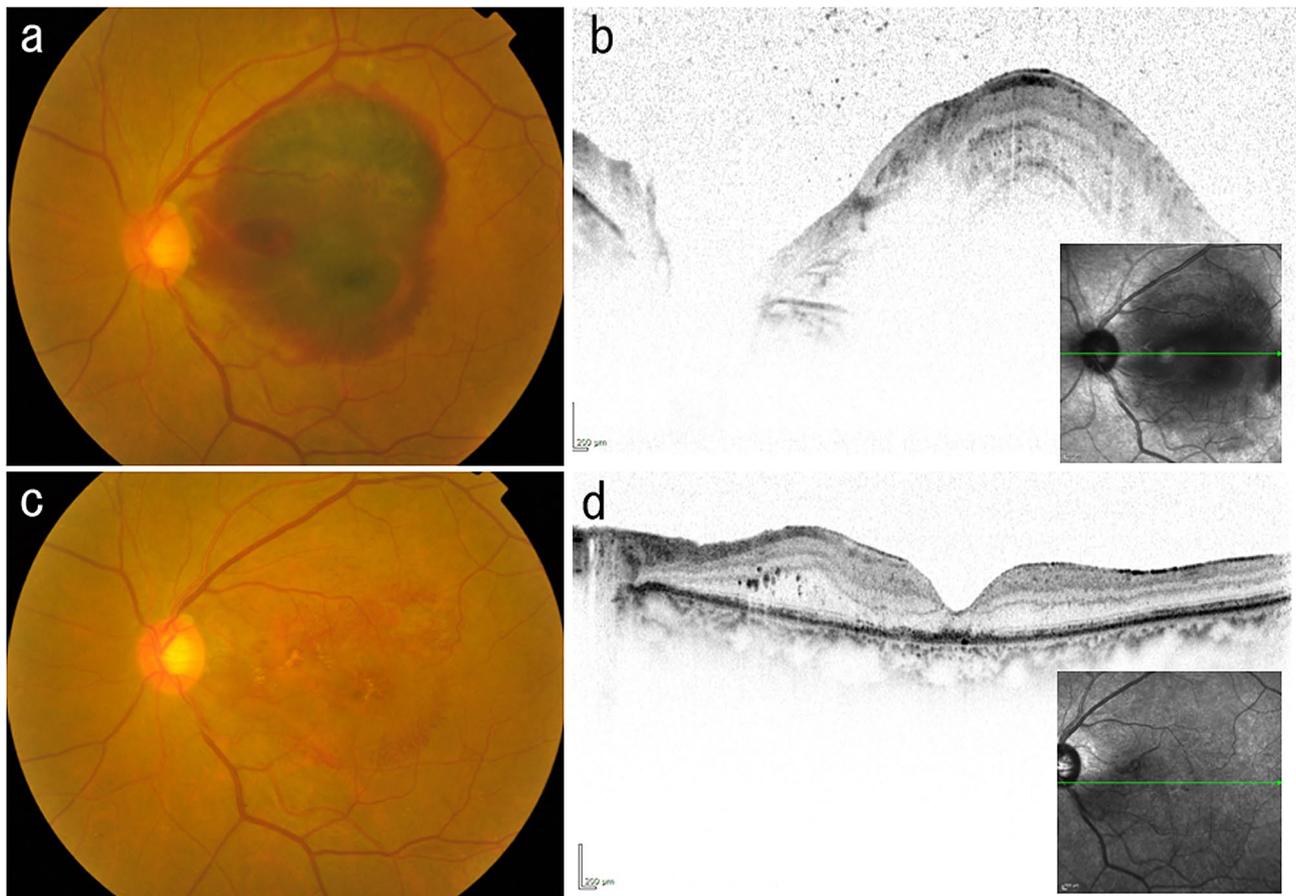


Fig. 2 Preoperative and postoperative findings of a case of subretinal hemorrhage. **a** Before surgery, a hemorrhage measuring 3.8 disc diameters and involving the fovea was observed. The Early Treatment Diabetic Retinopathy Study (ETDRS) score was 8. **b** The preoperative central retinal thickness (CRT) measured on optical coherence tomography (OCT) was 1223 μm . In this OCT, the images indicate

the location adjacent to the fovea. **c** The retinal hemorrhage was displaced by intravitreal injection of gas without recombinant tissue plasminogen activator. The 3-month postoperative ETDRS score was 58. **d** The 3-month postoperative CRT was 127 μm , and the central ellipsoid zone was undetectable

Discussion

In the present study, the strategy of anatomic site-oriented therapy using different treatments to target the hemorrhagic retinal layers observed on OCT was useful for macular hemorrhage secondary to RAM. We classified macular hemorrhage according to the anatomic site of the hemorrhage into subinternal limiting membrane hemorrhage, subretinal hemorrhage, intraretinal hemorrhage, and multilevel hemorrhage, and used differential treatments for the 4 types according to the characteristic of each type (anatomic site-oriented therapy).

For subinternal limiting membrane hemorrhage, we performed vitrectomy to peel the internal limiting membrane and remove the hemorrhage. At 3 months postsurgery, the mean ETDRS score had increased significantly from that at baseline, showing the greatest improvement among the 4 types of hemorrhage (Table 1). The mean

CRT had decreased significantly at 3 months postsurgery, and the mean 3-month postoperative CRT showed no thinning when compared with the fellow eyes. In addition, the central ellipsoid zone was detectable in all 7 eyes. Iijima and colleagues [27] conducted Nd:YAG laser photodisruption to treat 6 eyes with preretinal hemorrhage caused by RAM. They reported that whilst the treatment effectively dispersed the preretinal hemorrhage, resorption of the hemorrhage took time in eyes with subinternal limiting membrane hemorrhage and that visual recovery was less prominent in eyes that also had subretinal hemorrhage. Ulbig and colleagues [28] conducted Nd:YAG laser photodisruption in 21 eyes with premacular subhyaloid hemorrhage of various etiologies and reported that the visual acuity improved within 1 month in 16 eyes, whilst the vitreous opacity persisted in 4 eyes and required vitrectomy. They also reported complications including macular hole formation in 1 eye and development of retinal

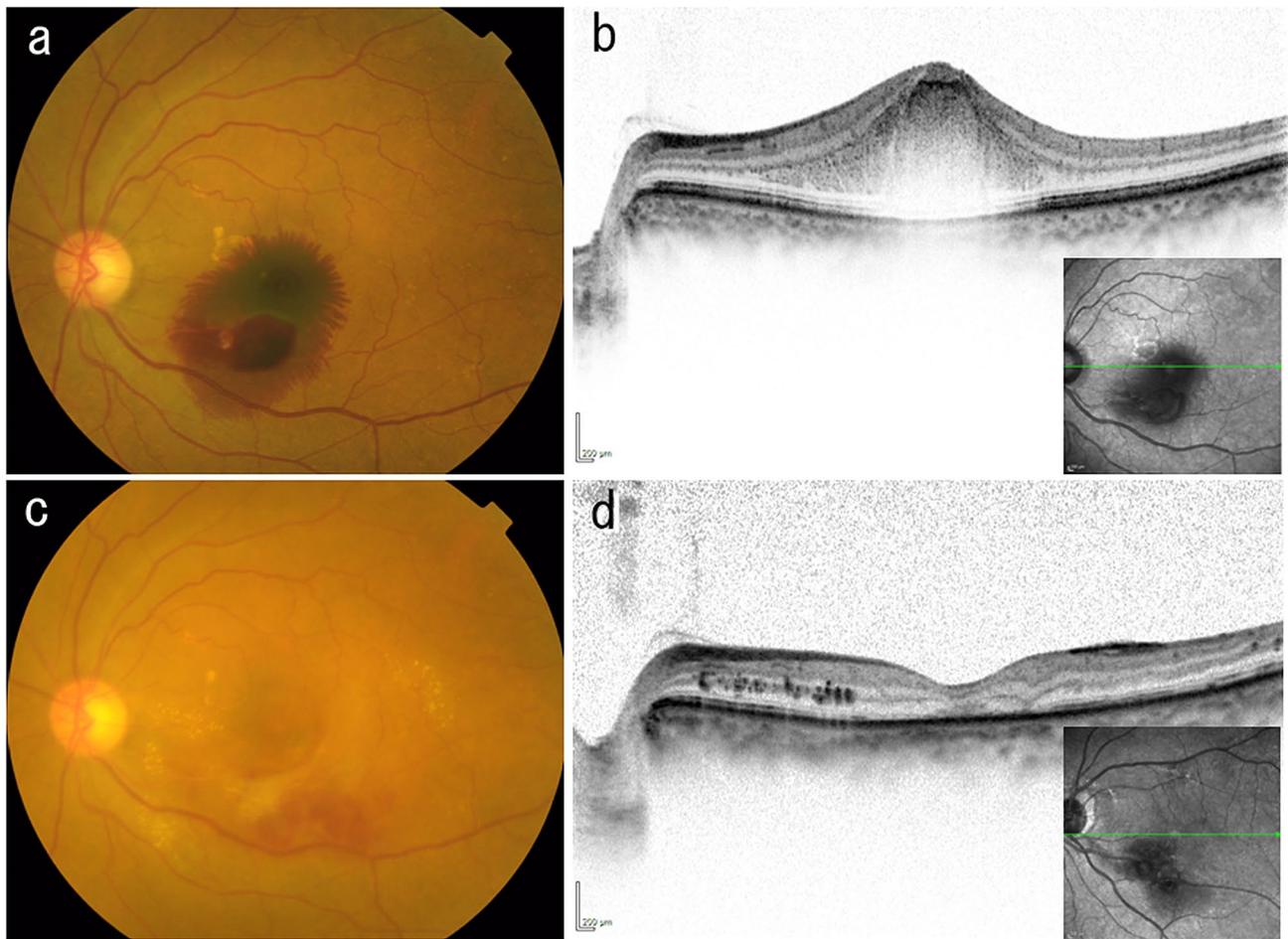


Fig. 3 Preoperative and postoperative findings of a case of intraretinal hemorrhage. **a** Before surgery, a hemorrhage measuring 2.8 disc diameters and involving the fovea was observed. The Early Treatment Diabetic Retinopathy Study (ETDRS) score was 34. **b** The preoperative central retinal thickness (CRT) measured on optical coherence tomography (OCT) was 637 μm . On OCT, the intraretinal hemorrhage appeared to be adjacent to the fovea, while a subinternal limiting

ing membrane hemorrhage was observed at the site of a retinal arterial microaneurysm. **c** The intraretinal hemorrhage was displaced by intravitreal injection of gas without recombinant tissue plasminogen activator. The intraretinal hemorrhage recurred after the surgery but resolved spontaneously. The 3-month postoperative ETDRS score was 50. **d** The 3-month postoperative CRT was 151 μm , and the central ellipsoid zone was undetectable

detachment at the site of the retinal break in 1 myopic eye. Internal limiting membrane peeling and hemorrhage removal by performing vitrectomy are technically simple and resulted in a favorable visual outcome. In eyes with subinternal limiting membrane hemorrhage, the central ellipsoid zone tends to be preserved before treatment and is characterized by good visual outcomes after treatment. For the 7 eyes in the present series, mild subfoveal hemorrhage was found during vitrectomy, and fluid/gas exchange was therefore performed. The subfoveal hemorrhage was masked by the presence of subinternal limiting membrane hemorrhage and detection was not possible before surgery. Hence, uncomplicated subinternal limiting membrane hemorrhage is generally treated with vitrectomy only, but if subfoveal hemorrhage is found during the vitrectomy, fluid/gas exchange should be considered.

For subretinal hemorrhage, we performed intravitreal injection of gas with or without rt-PA. However, the mean ETDRS score at 3 months postsurgery increased significantly but only mildly compared with the baseline score. The mean 3-month postoperative CRT also improved significantly when compared with the baseline score but was significantly thinner than that of the unaffected fellow eyes, and the central ellipsoid zone was undetectable in all 7 eyes. Kim and colleagues [21] reported significant thinning of the outer retinal layers in the regions affected by submacular hemorrhage, a finding that suggests that the hemorrhage induces marked damage in the outer retinal layers and explains the poor visual prognosis of submacular hemorrhage. Glatt and Machemer [22] and Benner and colleagues [23] recommended treatment within 7 days of onset of subretinal hemorrhage. Van Zeeburg and van

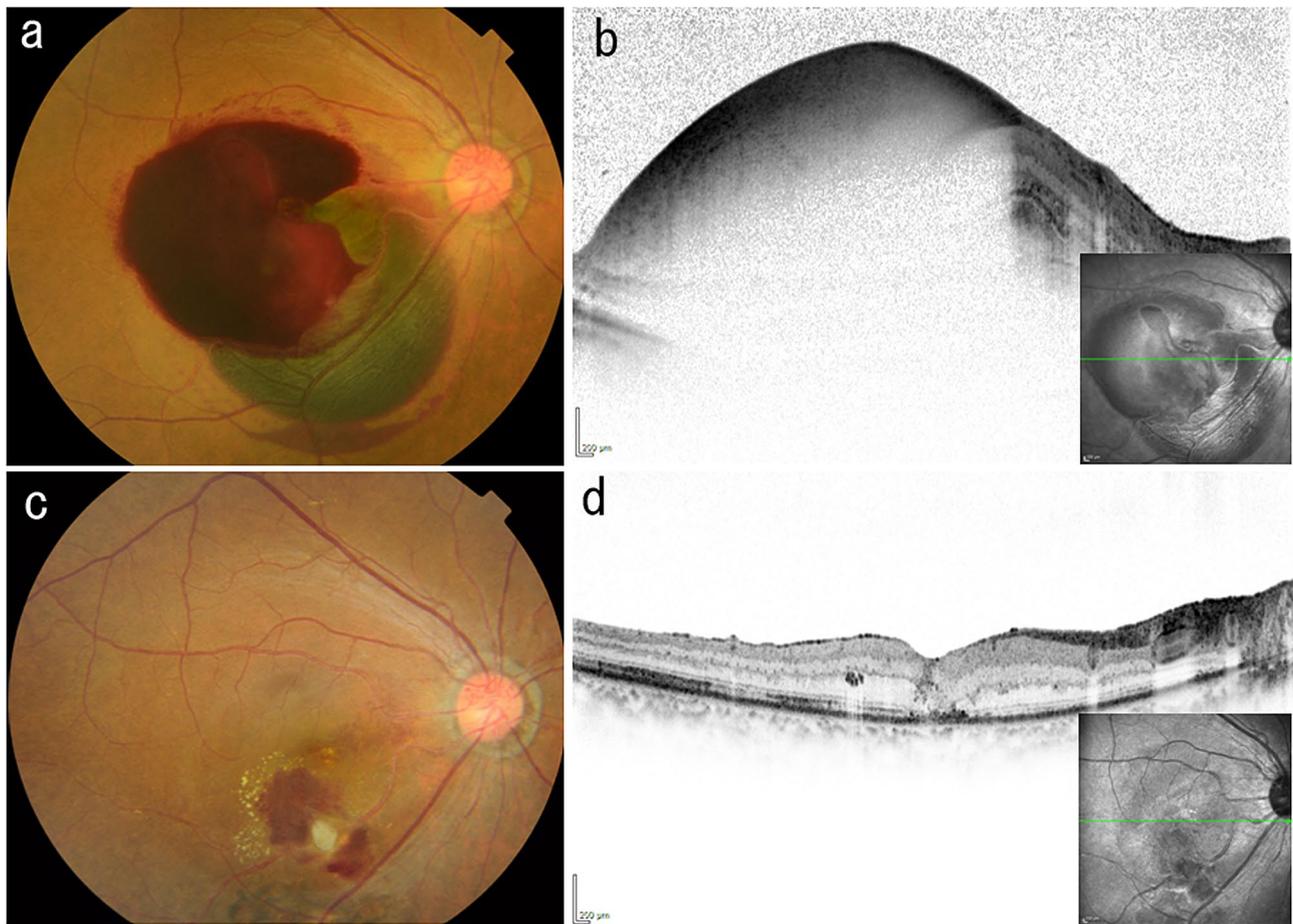


Fig. 4 Preoperative and postoperative findings of a case of multi-level hemorrhage. **a** Before surgery, a hemorrhage measuring 5.5 disc diameters and involving the fovea was observed. The Early Treatment Diabetic Retinopathy Study (ETDRS) score was 17. **b** The preoperative central retinal thickness (CRT) measured on optical coherence

tomography was 1549 μm . **c** The retinal hemorrhage was displaced/resolved by vitrectomy + fluid gas exchange. The 3-month postoperative ETDRS score was 35. **d** The 3-month postoperative CRT was 237 μm , and the central ellipsoid zone was undetectable

Meurs [20] reported no differences in efficacy and complications between “vitrectomizing techniques” and “non-vitrectomizing techniques” for submacular hemorrhage in AMD. Extrapolating from this finding, we assume that “vitrectomizing techniques” [4, 8, 9] and “nonvitrectomizing techniques” [13, 15] also do not differ in efficacy or complications for submacular hemorrhage secondary to RAM. However, further study is required to validate this assumption. In many facilities and for many ophthalmologists, “nonvitrectomizing techniques” have the advantage over “vitrectomizing techniques” from the viewpoint of the possibility of early treatment at the outpatient clinic. However, Mizutani and colleagues [15] treated 14 RMA eyes with intravitreal gas with or without rt-PA. Vitreous hemorrhage subsequently occurred in all 4 eyes treated with gas + rt-PA and in only 1 of the 10 eyes treated with gas alone, with a significant difference ($P < .005$). Therefore, when using intravitreal rt-PA in eyes with RAM, we

recommend conducting photocoagulation of the RAM 1 to 2 days before the intravitreal injection.

Among eyes with multilevel hemorrhage, 8 eyes had subinternal limiting membrane hemorrhage + subretinal hemorrhage, and 2 eyes had subinternal limiting membrane hemorrhage + intraretinal hemorrhage. Multilevel hemorrhage was characterized by large macular hemorrhage and large preoperative CRT. For the multilevel hemorrhage, we performed vitrectomy to peel the internal limiting membrane and remove the hemorrhage, followed by fluid gas exchange and then supine positioning to displace the subretinal hemorrhage. We did not use intravitreal or subretinal injection of rt-PA. This treatment strategy resulted in significant improvement in the visual acuity, but the postoperative CRT was significantly thinner than that of the unaffected fellow eyes, and the central ellipsoid zone was undetectable in all 10 eyes. In eyes with multilevel hemorrhage, the central ellipsoid zone is readily

Table 2 Operative procedure and complications

No.	Age (y), sex	Type	Procedure	Photo-coagulation	Other complications
1	72, M	SILMH	PEA + IOL + VIT + SF ₆	Intraop	-
2	85, M	SILMH	PEA + IOL + VIT + Air	No	-
3	75, F	SILMH	PEA + IOL + VIT + C ₃ F ₈	Intraop	-
4	67, F	SILMH	PEA + IOL + VIT + SF ₆	Intraop	-
5	69, F	SILMH	PEA + IOL + VIT + Air	Intraop	-
6	74, F	SILMH	PEA + IOL + VIT + Air	Intraop	-
7	84, F	SILMH	PEA + IOL + VIT + Air	No	-
8	55, F	SRH	rt-PA + C ₃ F ₈ IVI	Preop	-
9	82, F	SRH	rt-PA + C ₃ F ₈ IVI	Preop	-
10	79, F	SRH	rt-PA + C ₃ F ₈ IVI	Postop	-
11	66, M	SRH	rt-PA + C ₃ F ₈ IVI	Preop	-
12	70, M	SRH	C ₃ F ₈ IVI	Postop	-
13	77, F	SRH	C ₃ F ₈ IVI	No	-
14	82, F	SRH	C ₃ F ₈ IVI	No	-
15	80, F	IRH	C ₃ F ₈ IVI	No	IRH
16	84, M	IRH	C ₃ F ₈ IVI	Preop	-
17	87, F	IRH	C ₃ F ₈ IVI	No	-
18	87, F	Multilevel H	VIT+SF ₆	Preop	-
19	69, M	Multilevel H	PEA + IOL + VIT + Air	No	-
20	76, F	Multilevel H	PEA + IOL + VIT + SF ₆	Intraop	-
21	57, M	Multilevel H	PEA + IOL + VIT + SF ₆	No	-
22	78, F	Multilevel H	PEA + IOL + VIT + SF ₆	No	Mild VH
23	75, F	Multilevel H	PEA + IOL + VIT + SF ₆	Postop	-
24	74, F	Multilevel H	PEA + IOL + VIT + Air	Preop	Mild VH
25	72, F	Multilevel H	PEA + IOL + VIT	No	-
26	79, F	Multilevel H	PEA + IOL + VIT	No	-
27	83, F	Multilevel H	PEA + IOL + VIT	No	-

SILMH subinternal limiting membrane hemorrhage, *SRH* subretinal hemorrhage, *IRH* intraretinal hemorrhage, *Multilevel H* at least 2 among *SILMH*, *SRH*, and *IRH*, *PEA* phacoemulsification, *IOL* intraocular lens, *VIT* vitrectomy, *rt-PA* recombinant tissue plasminogen activator, *SF₆* sulfur hexafluoride, *C₃F₈* perfluoropropane, *IVI* intravitreal injection, *VH* vitreous hemorrhage, *IRH* intraretinal hemorrhage, *Intraop* intraoperative, *Preop* preoperative, *Postop* postoperative

damaged. If possible, vitrectomy should ideally be done within 7 days of disease onset. Sonmez and colleagues [9] conducted internal limiting membrane removal, subretinal injection of rt-PA, and fluid-air exchange within 7 days of symptom onset in 4 eyes with multilevel macular hemorrhage secondary to RAM. As a result, improvement in the visual acuity and in the CRT with a well-preserved foveal structure was achieved in all 4 eyes. Inoue and colleagues [8] performed internal limiting membrane removal, subretinal injection of rt-PA, and fluid-air/gas exchange in 22 eyes with macular hemorrhage associated with RAM but no subinternal limiting membrane hemorrhage at the fovea, and achieved improved visual acuity after the surgery. However, a macular hole was found intraoperatively in 2 eyes and postoperatively in 2 eyes. None of the patients in our series developed macular hole, which could be because we did not use subretinal rt-PA injection in any of them. Pichi and colleagues [29] and Sagara

and colleagues [30] reported that macular hole formation is commonly associated with RAM. Whether subretinal injection of rt-PA induces macular hole formation should be examined in further studies.

For intraretinal hemorrhage, we performed intravitreal gas injection without rt-PA. The mean ETDRS score at 3 months postoperatively had apparently increased from baseline, but the visual acuity had not significantly improved. Whilst the mean CRT at 3 months postoperatively had decreased from baseline with significant improvement, the postoperative CRT showed significant thinning when compared with that of the unaffected fellow eyes, and the central ellipsoid zone was undetectable. Intraretinal hemorrhage in RAM has not been reported. Intravitreal injection of anti-VEGF has been reported to be effective for the treatment of RAM with hard exudate in 38 eyes reported by Pichi and colleagues [31] and in 23 eyes reported by Cho and colleagues [32]. We plan to examine the effectiveness of intravitreal anti-VEGF+gas

injection for the treatment of intraretinal hemorrhage in a future study.

In this series, we treated RAM with laser photocoagulation except when the RAM was located near the macula, aiming to prevent recurrence. However, the effectiveness of photocoagulation was not determined owing to the absence of controls. In addition, it should be noted that development of aneurysms in the retina is related to high blood pressure attacks [33], and controlling blood pressure is important for preventing RAM rupture.

Subretinal injection of rt-PA for the treatment of macular hemorrhage has been reported to result in macular hole formation in 18% of the cases (4/22 eyes) [8]. The present study was characterized by use of anatomic site-oriented therapy without subretinal rt-PA injection, resulting in no postoperative macular hole formation. The methods we used have the additional merit of being technically simple. However, a limitation of the present study is the absence of untreated controls. Furthermore, the optimal treatment methods for individual hemorrhagic retinal layers require further studies. A prospective study with a large number of cases is warranted to validate the usefulness of anatomic site-oriented therapy without subretinal drug injection for the treatment of macular hemorrhage secondary to RAM.

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