Title

Impact of macular intraretinal hemorrhage and macular hole on the visual prognosis of submacular hemorrhage due to retinal arterial macroaneurysm rupture

Abbreviated title

Ruptured retinal arterial macroaneurysm

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Brief summary statement

Both macular intraretinal hemorrhage and macular hole were poor prognostic indicators in cases with submacular hemorrhage due to retinal arterial macroaneurysm rupture.

Abstract

Purpose: To compare the effects of macular intraretinal hemorrhage (IRH) and macular hole (MH) on best-corrected visual acuity (BCVA) after displacement of submacular hemorrhage (SMH) due to retinal arterial macroaneurysm (RAM) rupture.

Methods: This multicenter retrospective study included 48 eyes with SMH due to RAM rupture. Cases underwent vitrectomy to displace SMH and were followed up for 6 months. We classified cases according to the presence of IRH and MH and compared the postoperative BCVA among the groups.

Results: We classified the eyes into IRH(+)MH(+) group (10 eyes), IRH(+)MH(−) group (23 eyes), and IRH(−)MH(−) group (15 eyes). The postoperative BCVA was significantly worse in the IRH(+)MH(+) and IRH(+)MH(−) than in the IRH(−)MH(−) (0.91 ± 0.41 in logarithm of the minimal angle of resolution units, Snellen equivalent 20/163, 0.87 ± 0.45, 20/148, and 0.18 ± 0.21, 20/30, respectively; $P < 0.001$). The postoperative CRT was significantly lower in the IRH(+) group (IRH(+)MH(+) and IRH(+)MH(−) groups combined) than in the IRH(−) group (IRH(−)MH(−) group) (121.4 ± 70.1 μm and 174.3 ± 32.9 μm, respectively, $P = 0.008$). The postoperative ELM and EZ continuities were significantly discontinuous in the IRH(+) group ($P < 0.001$, $P = 0.001$, respectively). The multiple linear regression analysis showed that both IRH(+)MH(+) and IRH(+)MH(−) were associated with the postoperative BCVA (regression coefficient, 0.799 and 0.711, respectively ; P < 0.001 for both).

Conclusions: Both IRH and MH were poor prognostic indicators in cases with SMH due to RAM rupture.

Introduction

Retinal arterial macroaneurysm (RAM) is an acquired, focal dilation of an arteriole, usually within the first three orders of the retinal arterial system.[1,2] It is more common in the elderly, particularly women with underlying hypertension and atherosclerosis, and past reports suggest a prevalence of 1 in 1,500 to 4,500 persons.[3,4] Hemorrhage due to RAM rupture can occur in any space, including the subretinal, intraretinal, sub-internal limiting membrane (ILM), preretinal spaces, and the vitreous cavity. If the hemorrhage extends to the macula, it causes rapid vision loss.[5-7] In particular, submacular hemorrhage (SMH) causes severe damage to photoreceptor cells and induces apoptosis due to hemotoxicity and an insufficient supply of nutrients and oxygen.[8-11] Therefore, it is necessary to displace the hemorrhage from the submacular region to the region outside the macula as early as possible. In recent years, pneumatic displacement of SMH has frequently been performed, and the procedure is divided into two major techniques: vitrectomizing and nonvitrectomizing techniques. With regards to the vitrectomizing technique in particular, several reports have shown that a combination of vitrectomy and subretinal injection of tissue plasminogen activator (t-PA), which liquefies SMH, can reliably displace SMH.[12-15]

Complications of macular hole (MH) and intraretinal hemorrhage (IRH) have been reported as major factors that affect the visual prognosis after vitrectomizing pneumatic displacement of SMH combined with subretinal injection of t-PA.[16,17] It has been reported that MH is often associated with SMH due to RAM rupture[18,19]; in such patients, the visual prognosis is poor even if SMH is successfully displaced.[20] With regards to macular IRH, we recently performed a study using swept-source optical coherence tomography (SS-OCT) and showed that some cases of SMH due to RAM rupture are complicated by IRH in the macula; the visual prognosis of such cases was significantly worse than that of cases without IRH in the macula.[17] However, that was a single-center study with a small sample size; therefore, the magnitude of the effects of macular IRH on the visual acuity after SMH displacement was not fully elucidated in comparison with the effect of MH. Accordingly, the aim of the present multicenter study was to compare the effects of macular IRH and MH on the visual acuity after displacement of SMH due to RAM rupture.

Methods

This multicenter retrospective study included 48 eyes with SMH due to RAM rupture that was treated by pars plana vitrectomy with subretinal injection of t-PA and air or gas tamponade between September 2013 and Jun 2019 at Okayama University Hospital, Kyorin University Hospital, Tane Memorial Eye Hospital, Fukui Red Cross Hospital, Fukuoka University Chikushi Hospital, Kobe University Hospital, or Otowa Eye Center. The study protocol was in accordance with the Declaration of Helsinki, and institutional review board approval was obtained. All included patients were informed about the surgeries, including their risks and benefits, before they provided written consent.

We performed comprehensive ophthalmologic examinations for all patients before and 1 and 6 months after the surgery. These examinations included measurement of the best-corrected visual acuity (BCVA) with refraction using the 5-m Landolt C acuity chart and indirect and contact lens slit-lamp biomicroscopy. We recorded the visual acuity as a decimal value and converted it to the logarithm of the minimal angle of resolution (logMAR) unit. All eyes were examined by one of the following optical coherence tomography (OCT) devices: Triton (Topcon, Tokyo, Japan), Spectralis (Heidelberg Engineering, Heidelberg, Germany), or CIRRUS (Carl Zeiss Meditec, Dublin, CA, USA).

The diagnosis of SMH due to RAM was based on fundus examination, fundus photography, OCT, and/or fluorescein/indocyanine green angiography. The inclusion criteria were as follows: SMH due to RAM rupture; presence of SMH with a maximum central retinal thickness (CRT) of >500 μm, as measured by OCT; and follow-up for >6 months.[17] The exclusion criteria were as follows: inability to have preoperative OCT for macular retinal structure evaluation because of vitreous hemorrhage, preretinal hemorrhage (PRH), and/or sub-ILM hemorrhage; presence of organized SMH, which is white and/or fibrous in appearance, as determined by fundus examination; and any previous history of other diseases of the retina, choroid, or optic nerve.

We retrospectively retrieved the following data using the patients' records: age, sex, days from diagnosis to surgery, BCVA (preoperative and postoperative at 1 and 6 months), postoperative CRT at 6 months, postoperative ELM and EZ continuities at 6 months, and development of MH. Development of MH was defined by confirmation of the presence of MH on preoperative or early postoperative OCT or intraoperative confirmation of the presence of MH by the surgeon. CRT was measured by at least two retinal specialists at each facility using the caliper function of the software provided with the OCT. Three retinal specialists (S.D.,S.K., and Y.M.) analyzed the color fundus photographs (presence or absence of fluffy sign) and B-scan images (presence or absence of macular IRH, continuity of ELM and EZ).

We performed displacement of SMH as soon as possible after the diagnosis of SMH due to RAM rupture, according to previous reports.[12,14,17] All patients underwent microincision vitrectomy with a 25-gauge system, and all patients with lens were treated with simultaneous phacoemulsification and intraocular lens insertion. After vitrectomy, we injected 4000 IU t-PA (GRTPA; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan or Cleactor; Eisai, Co. Ltd., Tokyo, Japan) in 0.1 mL into the retina using a 41-gauge subretinal infusion needle (MedOne, Sarasota, FL) for SMH liquefaction. Intraoperative photocoagulation was applied to treat RAM at the discretion of the surgeon. In cases with sub-ILM hemorrhage, we removed the hemorrhage after removal of ILM on the sub-ILM hemorrhage. We performed ILM peeling in cases of MH. Before completing the surgery, fluid–air or fluid–20% sulfur hexafluoride exchange was performed in all cases at the discretion of the surgeon. Patients were instructed to maintain a face-down position for several days; the duration varied among facilities. Patients with MH maintained a facedown position until we confirmed MH closure using OCT.

Statistical analysis

Data are presented as mean values ± standard deviations. To compare the characteristics of patients and surgical outcomes among groups, we used one-way analysis of variance with the Games–Howell post hoc test and Pearson's chi-square test for continuous variables and categorical variables, respectively. We also examined factors associated with the postoperative BCVA at 6 months using multiple linear regression analysis. A P-value of <0.05 (two-tailed) was considered statistically significant. We performed all statistical analyses using the Statistical Package for the Social Sciences software (SPSS, version 22.0; IBM Corporation, Armonk, NY).

Results

Table 1 shows the baseline characteristics and surgical outcomes of the 48 patients (38 female and 10 male patients) enrolled in this study. The mean age of the patients was 80.6 ± 8.6 years. None of the 48 cases received prior treatment, such as anti-VEGF injections or photocoagulation, for SMH due to RAM rupture. After surgery, SMH was successfully displaced out of the macula in all cases, and no case showed residual SMH on B-scan OCT images at 6 months after surgery. Surgical complications included postoperative VH in two cases: one case was in the IRH(+)MH(+) group and was treated with additional vitreous cavity lavage, resulting in postoperative BCVA at 6 months of 20/1000; the other case was in the IRH(-)MH(-) group and underwent a total of three additional vitreous cavity lavages, resulting in postoperative BCVA at 6 months of 20/28. Relative to the baseline BCVA (1.24 ± 0.53 in logMAR units, Snellen equivalent 20/348), the mean BCVA significantly improved at both 1 month and 6 months after the surgery (0.80 ± 0.42, 20/126, and 0.66 ± 0.50, 20/91, respectively, both $P < 0.01$; Figure 1).

We analyzed preoperative OCT B-scan images of SMH due to RAM rupture and observed the presence of macular IRH in 33 of 48 eyes (68.8%). Using the B-scan OCT images, as previously reported, we detected macular IRH in the Henle fiber layer in all 33 cases (Fig. 2).[17] In addition, fluffy hemorrhage (fluffy sign; Fig. 2) were observed on color fundus photographs of 22 of the 33 cases; in all 22 of the 33 cases, fluffy hemorrhage corresponded to macular IRH on OCT B-scan images, as previously reported (Fig. 2).[17]

MH developed in 10 of the 48 eyes (20.8%; Table 1); it was preoperatively confirmed in one eye and intraoperatively confirmed in eight eyes. Although MH was closed after the initial surgery in seven eyes, additional surgery for MH closure was required in two eyes. One case underwent additional vitrectomy with ILM inversion and gas tamponade to close the MH. Postoperative BCVA at 6 months was 20/33. In another case, additional vitrectomy with ILM transplantation and gas tamponade were performed to close the MH since the ILM was peeled at the initial surgery. The postoperative BCVA at 6 months was 20/132. In a separate case, MH developed postoperatively in one eye which was in the IRH(+)MH(+) group. Additional vitrectomy with ILM peeling and gas tamponade were performed and MH was closed. Postoperative BCVA at 6 months was 20/132 for the latter case.

We divided 48 eyes into the following three groups according to the presence or absence of macular IRH and MH: IRH(+) MH(+)(10 eyes; 20.8%), IRH(+) MH(−) (23 eyes; 47.9%), and IRH(−) MH (−) (15 eyes; 31.3%) groups. There were no eyes in the IRH(−)

MH(+) group. Table 2 shows the patient characteristics and surgical outcomes in each group. There was no significant difference in the preoperative visual acuity among the three groups (P = 0.342), although the IRH(+) MH(+) group and the IRH(+) MH(−) group showed significantly worse visual acuity than did the IRH(−) MH(−) groups at 1 month (0.92 ± 0.22, 20/166, 1.01 ± 0.36, 20/205, and 0.42 ± 0.34, 20/53, respectively; P < 0.001) and 6 months (0.91 ± 0.41, 20/163, 0.87 ± 0.45, 20/148, and 0.18 ± 0.21, 20/30, respectively; P < 0.001) after surgery. There was no significant difference in the postoperative BCVA at 1 and 6 months between the IRH(+) MH(+) and IRH(+) MH(−) groups (P = 0.673 and P = 0.974, respectively). The CRT at 6 months after surgery was significantly different among the three groups; it was significantly lesser in the IRH(+) MH(+) group than in the IRH(−) MH(−) group (99.5 ± 46.0 μm and 174.3 ± 32.9 μm, respectively; P = 0.001). The IRH(+) MH(−) group showed a trend of thinning compared with the IRH(−) MH(−) group, although the difference was not significant (130.9 ± 77.3 μm and 174.3 ± 32.9 μm, respectively; P = 0.059). When all eyes were divided into two groups based on the presence or absence of macular IRH, the postoperative BCVA was significantly worse and CRT was significantly lower. Additionally, ELM and EZ were significantly discontinuous at 6 months in the IRH(+) group (IRH(+) MH(+) and IRH(+) MH(−) groups combined) than in the IRH(−) group (IRH(−) MH(−) group) (BCVA: 0.88 ± 0.43, 20/152, and 0.18 ± 0.21, 20/30, respectively, P < 0.001;

CRT: 121.4 ± 70.1 μm and 174.3 ± 32.9 μm, respectively, $P = 0.008$; ELM status, $P < 0.001$; EZ status, $P = 0.001$). The percentage of cases with the fluffy sign (Fig. 2) was significantly higher in the IRH(+) MH(+) (50%) and IRH(+) MH(−) (73.9%) groups than in the IRH(−) MH(−) group (0%; $P < 0.001$ and $P = 0.002$, respectively). However, there was no significant difference between the IRH(+) MH(+) and IRH(+) MH(−) groups ($P = 0.240$).

We then used multiple regression analysis to estimate the difference in the postoperative BCVA at 6 months between the IRH(+) MH(+) and IRH(+) MH(−) groups and the IRH(−) MH(−) group. In Model 1, we entered two binary explanatory variables; one takes 1 if the IRH(+) MH(+) group and 0 otherwise, while the other takes 1 if the IRH(+) MH(-) group and 0 otherwise. In Model 2, we further added age, sex, and the preoperative BCVA as explanatory variables. In both models, both the IRH(+) MH(+) and IRH(+) MH(−) groups showed significantly worse postoperative BCVA at 6 months than did the IRH(−) MH(−) group (Table 3). In models 1 and 2, the partial regression coefficients of the IRH(+) MH(+) and IRH(+) MH(−) groups were comparable (model 1: 0.730 and 0.695, respectively; model 2: 0.799 and 0.711, respectively). The regression coefficient of age in model 2 was only 0.013, although age was significantly associated with the postoperative BCVA at 6 months. We then performed multiple regression analysis in the same manner for the 41 eyes that did not receive intraoperative photocoagulation for RAM (See Table, Supplemental Digital Content 1). The results had a similar trend to those of the multiple regression analysis performed for all cases.

Representative cases from the IRH(+) MH(+), IRH(+) MH(−), and IRH(−) MH(−) groups are shown in Figures 3, 4, and 5, respectively.

Discussion

In this multicenter retrospective study, we investigated 48 eyes with SMH due to RAM rupture that were treated by vitrectomy, subretinal t-PA injection, and fluid–gas exchange for SMH displacement and estimated the impact of macular IRH and MH on the postoperative visual acuity. Although MH has been reported as an important factor affecting the visual acuity after SMH displacement,[16,19,20,21] our multiple linear regression analysis (Table 3) showed that the visual prognosis of cases with macular IRH was poor after SMH displacement, regardless of the presence or absence of MH. This finding indicates the magnitude of the effect of macular IRH on the visual prognosis after displacement of SMH due to RAM rupture.

In the present study, 10 of 33 eyes (30.3%) with macular IRH developed MH (Table 2). Meanwhile, all eyes without macular IRH did not develop MH. Furthermore, the presence of macular IRH resulted in a decreased postoperative CRT (Table 2). Thus, eyes with macular IRH are more likely to develop MH with a decrease in CRT, which result in a poor visual prognosis (Table 2). The mechanism underlying macular IRH formation may be involved in the poor visual prognosis in such cases. RAM rupture causes blood to flow into the subretinal space, and if the pressure in the subretinal space becomes high enough to penetrate the sensory retina at the fovea, but not high enough to penetrate ILM, the blood would flow into the Henle fiber layer, which is a sparse layer with few cellular components, and form macular IRH (Fig. 6). As shown in Figure 2B and Figure 3C, when blood flows into the Henle fiber layer, the pressure from the subretinal space considerably reduces the foveal thickness. It is believed that ILM is damaged at the time of macular IRH formation or gradually disrupted on exposure to blood, resulting in the formation of MH.[18]

In cases of SMH caused by RAM rupture, another possible mechanism underlying macular IRH formation is that the hemorrhage from the ruptured RAM flows directly into the Henle fiber layer (see Figure, Supplemental Digital Content 2, which shows a representative case). In our experience, formation of IRH via this mechanism is much less frequent than the formation of macular IRH via the SMH-mediated mechanism described above. Factors possibly related to direct blood flow from the ruptured RAM into the Henle fiber layer include the depth of RAM in the retina, distance from the fovea to RAM, direction of the ruptured wall of RAM, and the bleeding pressure from RAM. The visual prognosis of cases with macular IRH caused by this mechanism is unknown and requires further study.

In this study, the fluffy sign,[17] which is a fundus finding specific to IRH (Fig. 2), was observed in 50% cases in the IRH(+) MH(+) group and 73.9% cases in the IRH(+) MH(−) group. Although the fluffy sign is a very useful finding for the detection of macular IRH without the use of high-penetration OCT, it was not observed in all cases of IRH in the present study, possibly because the fluffy sign cannot be observed if it is covered by dense vitreous hemorrhage, extensive PRH, or sub-ILM hemorrhage. In such cases, the presence or absence of IRH should be evaluated using high-penetration OCT, such as SS-OCT.

This study has some limitations. First, it was a retrospective study with a relatively small sample size. Second, there were variations among facilities in tamponade substances, the types of t-PA and the duration of the prone positioning. Third, information pertaining to the period from SMH onset to surgery was missing. Fourth, selection bias may have existed because cases with difficulty in assessment of the internal structure of the retina using preoperative OCT were excluded. Fifth, there was no case of MH in the absence of IRH [IRH(−) MH(+) group]; such cases were possibly excluded because vitreous hemorrhage, PRH, and/or sub-ILM hemorrhage caused difficulties in assessment of the internal retinal structures using preoperative OCT. Sixth, there is no comparison with nonsurgical cases. Seventh, the relationship between IRH size and visual prognosis has not been verified due to the difficulty of accurately in measuring IRH size with the current OCT technology. Eighth, there were two cases in which the MH was unclosed after the initial surgery, one case with postoperative MH, and two cases with postoperative VH. Since additional surgery was performed on these cases, this may have affected postoperative visual prognosis. Ninth, multiple OCT machines were used.

In conclusion, the results of this multicenter study suggest that macular IRH and MH result in poor visual outcomes after displacement of SMH associated with RAM rupture. Because of the significant impact of macular IRH and MH on visual prognosis, clinicians need to evaluate for their presence or absence before performing displacement of SMH due to RAM rupture. If macular IRH and MH are present, the patient should be informed prior to surgery that postoperative vision is unlikely to improve significantly. A prospective clinical study involving a larger number of patients is necessary to confirm our findings.

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Figure legends

Figure 1 Graph showing the best-corrected visual acuity (BCVA) at baseline, 1 month, and 6 months after surgery for submacular hemorrhage (SMH) due to retinal arterial macroaneurysm (RAM) rupture

Error bars represent standard deviations.

log MAR, logarithm of the minimal angle of resolution

$^{*}P < 0.01$

Figure 2 Representative fundus photograph and optical coherence tomography (OCT) B-scan images of macular intraretinal hemorrhage (IRH) and the associated fluffy sign

A. Fundus photograph of SMH associated with retinal arterial macroaneurysm (RAM) rupture

The arrow shows RAM and the arrowheads show the fluffy sign, which matches the contour of the macular IRH spreading radially from the fovea.

B. Vertical B-scan image of SMH and macular IRH due to RAM rupture

The arrow indicates the very thin foveal retina.

C. Horizontal B-scan image of SMH and macular IRH due to RAM rupture

D-F. A schematic image of the hemorrhagic area shows the correspondence between the color fundus photograph (A) and OCT B-scan images (B and C). The gray area indicates SMH, and the checkered area indicates macular IRH. The black lines in D indicate the locations corresponding to those in the vertical and horizontal B-scan images. The white continuous lines in D, E, and F indicate the bilateral margins of the macular IRH in E and F, and the white dotted lines indicate the bilateral margins of SMH in E and F. The macular IRH is localized at the Henle fiber layer (E and F).

Figure 3 Representative case involving a 62-year-old woman with submacular hemorrhage (SMH), macular intraretinal hemorrhage (IRH), and macular hole (MH) due to retinal arterial macroaneurysm (RAM) rupture

A. A fundus photograph obtained before displacement of SMH shows RAM (white arrowhead), preretinal hemorrhage (PRH; dotted area), SMH (white arrow), and the fluffy sign (black arrowheads), which represents macular IRH.

B and C. Horizontal (B) and vertical (C) optical coherence tomography (OCT) images obtained before displacement of SMH show SMH (asterisks) and macular IRH localized at the Henle fiber layer (white arrows). The yellow arrow indicates the very thin foveal retina. Internal limiting membrane peeling was performed because MH was recognized during surgery; it was not detected on preoperative OCT images.

D. A fundus photograph obtained at 1 month after displacement of SMH shows that the majority of SMH has been displaced outside the macular area.

E and F. Horizontal (E) and vertical (F) OCT images obtained at 1 month after displacement of SMH show disappearance of PRH, SMH and IRH. The white arrows indicate thinning of the fovea (central retinal thickness = 78 μm) and disruption of the ellipsoid zone. Although the best-corrected visual acuity at 1 month after the surgery (20/100) improved relative to the preoperative visual acuity (20/133), it remained low.

Figure 4 Representative case involving an 80-year-old woman with submacular hemorrhage (SMH) and macular intraretinal hemorrhage (IRH), without macular hole, due to retinal arterial macroaneurysm (RAM) rupture

A. A fundus photograph obtained before displacement of SMH shows preretinal hemorrhage (PRH; arrow) adjacent to RAM (white arrowhead) and the fluffy sign (black arrowheads) spreading radially from the fovea.

B and C. Horizontal (B) and vertical (C) optical coherence tomography (OCT) images obtained before displacement of SMH show SMH (asterisks) and macular IRH localized in the Henle fiber layer around the macula (arrows).

D. A fundus photograph obtained at 3 months after displacement of SMH shows that the majority of SMH is displaced outside the macular area.

E and F. Horizontal (E) and vertical (F) OCT images obtained at 3 months after displacement of SMH show disappearance of PRH, SMH, and IRH. The arrows indicate thinning of the fovea (central retinal thickness = 48 μm) and disruption of the ellipsoid zone. Although the best-corrected visual acuity at 3 months after surgery (20/667) improved relative to the preoperative visual acuity (20/2000), it remained low.

Figure 5 Representative case involving a 63-year-old woman with submacular hemorrhage (SMH), without macular intraretinal hemorrhage (IRH) and macular hole, due to retinal arterial macroaneurysm (RAM) rupture

A. A fundus photograph obtained before displacement of SMH shows preretinal hemorrhage (PRH; arrow) adjacent to RAM (arrowhead).

B and C. Horizontal (B) and vertical (C) optical coherence tomography (OCT) images before displacement of SMH indicate SMH (asterisks). Macular IRH is not detected.

D. A fundus photograph obtained at 3 months after displacement of SMH shows that SMH is displaced outside the macular area.

E and F. Horizontal (E) and vertical (F) OCT images obtained at 3 months after displacement of SMH show complete disappearance of SMH. The central retinal thickness is 149 μm, and the retinal outer layer structure at the fovea is continuous (arrows in E and F). The best corrected visual acuity at 3 months after surgery (20/17) improved relative to the preoperative visual acuity (20/29).

Figure 6 Schematic drawings showing the possible pathological mechanism underlying macular intraretinal hemorrhage (IRH)

The arrowhead shows a ruptured retinal arterial macroaneurysm (RAM). The arrows show the directions of blood flow. First, the blood flows from RAM into the subretinal space to form SMH. As the volume of SMH increases, the subretinal pressure increases, resulting in perforation of the outer retinal layer at the fovea. Subsequently, the blood flows into the Henle fiber layer, which has less tissue resistance than does the outer nuclear layer, to form macular IRH.

Supplemental Digital Content 1. docx

Supplemental Digital Content 2. tif