Title

Adverse effect of macular intraretinal hemorrhage on the prognosis of submacular hemorrhage due to retinal arterial macroaneurysm rupture

Abbreviated title

Ruptured retinal arterial macroaneurysm

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Competing interests

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Keywords

macular intraretinal hemorrhage, retinal arterial macroaneurysm, submacular hemorrhage, subretinal hemorrhage, subretinal injection, tissue plasminogen activator

Brief summary statement

We investigated the clinical course of displacement of submacular hemorrhage (SMH) due to ruptured retinal arterial macroaneurysm using swept source optical coherence tomography and found that preoperative macular intraretinal hemorrhage is a novel poor prognostic factor for SMH displacement.

Abstract

Purpose: To investigate the clinical course of submacular hemorrhage (SMH) associated with ruptured retinal arterial macroaneurysm (RAM) using swept source optical coherence tomography (SS-OCT).

Methods: This study included 23 eyes of 23 consecutive patients diagnosed with SMH associated with ruptured RAM. Cases underwent displacement of SMH (vitrectomy + subretinal injection of tissue plasminogen activator + air tamponade) and were followed up for six months after surgery. Localization of the preoperative hemorrhage and its effect on pre and postoperative best-corrected visual acuity (BCVA), central retinal thickness (CRT), and continuity of the ellipsoid zone (EZ) were measured.

Results: Macular intraretinal hemorrhage (IRH) was observed in 17 eyes (73.9%, IRH (+) group) and was not observed in 6 eyes (26.1%, IRH (-) group). The IRH (+) group showed worse postoperative BCVA values compared with the IRH (-) group (0.89 ± 0.47 in logarithm of the minimal angle of resolution units, Snellen equivalent 20/155 and 0.16 ± 0.23, 20/29, respectively; $P < .01$), smaller CRT values (97.7 ± 53.5 μm, 173.0 ± 32.3 μm, respectively; $P < .01$), and a higher rate of EZ disruption (100%, 33.3%, respectively; $P < .01$).

Conclusion: Patients with preoperative macular IRH showed lower postoperative visual acuity and worse macular contour after SMH displacement compared with patients without macular IRH.

Introduction

Retinal arterial macroaneurysm (RAM) is a disease typically found in elderly people, especially females, which develops due to hypertension and arteriosclerosis.[1,2] RAM can lead to visual loss due to hemorrhage following macroaneurysm rupture, macular edema, and/or serous retinal detachment due to the vascular hyperpermeability of the RAM.[3-5] In particular, decreased visual acuity due to ruptured RAM can be sudden and severe.[6-8]

Vitrectomy to remove hemorrhage has been reported to lead to good visual prognosis in cases where bleeding from the ruptured RAM occurs in either vitreous cavity, the preretina or the sub-inner limiting membrane (ILM) space. [9,10] If bleeding occurs in the submacular space, observation without treatment can result in severe and permanent vision impairment due to toxicity from blood[11] as well as an insufficient supply of nutrients and oxygen. Therefore, removal of the submacular hemorrhage (SMH) or displacement of the SMH to the outside of the macular area is required.[10,12-14] Recently, displacement of SMH after liquefying the SMH with t-PA has been reported to be a safe and effective procedure.[15-19]

There are two main challenges regarding surgery and postoperative visual prognosis for SMH due to ruptured RAM. The first challenge is that the degree of best corrected visual acuity (BCVA) improvement after the displacement of SMH varies greatly between individual cases.[17,18] Unlike in cases of SMH due to age-related macular degeneration,[20,21] it is possible to predict with high probability whether the macula is abnormal prior to RAM rupture. Therefore, it should theoretically be possible to predict whether successful displacement of SMH soon after RAM rupture would result in a good visual prognosis.[13,14,17] However, it has been reported that, for unknown reasons, not all cases of SMH due to ruptured RAM show sufficient BCVA improvement following displacement of SMH. The second challenge is that it is difficult to determine both the preoperative macular structure as well as the preoperative localization of the hemorrhage at the macula. As reported previously, hemorrhage due to ruptured RAM, including cases with SMH, can be localized in any layer of the retina.[1,6,7,22] However, in many cases the preoperative macular structure, including the localization of the hemorrhage, are masked by complicating vitreous hemorrhage, preretinal and sub ILM hemorrhage. Therefore, it is impossible to evaluate the effect of surgery on the structure of the macula and the localization of the hemorrhage.

Recently, swept source optical coherence tomography (SS-OCT) has made it possible to obtain high-penetration and high-speed scans, which are difficult to obtain using spectral domain OCT. Thus, it is now possible to obtain high resolution tomographic slices from the retina through the sclera.[23,24] In this study, we utilized SS-OCT to visualize the macular structure, including hemorrhage localization, before and after displacement of SMH. We then investigated the relationships between pre and postoperative macular structures and postoperative BCVA.

Methods

Study design

All methods in this retrospective, nonrandomized interventional case series adhered to the tenets of the Declaration of Helsinki. Each patient was informed of the risks and benefits of both the surgical procedure and participation in this research study. Written informed consent for the surgery and for participation in the study was obtained from each patient. The study was approved by the institutional review board of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences.

Subjects

Twenty-three eyes of 23 consecutive patients with SMH attributable to ruptured RAM who were diagnosed between July 1, 2013 and April 30, 2017 were recruited for this study. The diagnosis of SMH due to RAM was based on fundus examination, fundus photography, SS-OCT, and/or fluorescein/indocyanine green angiography. The inclusion criteria were as follows: (1) SMH attributable to ruptured RAM; (2) presence of an SMH with a maximum height from the retinal pigment epithelium of more than 500 μm, as measured by SS-OCT; and (3) presence of unorganized SMH, as determined by fundus examination. We considered organized SMH to be white and/or fibrous in appearance. Cases for which the macular retinal structure could not be evaluated because of preoperative vitreous hemorrhage, preretinal hemorrhage, and/or sub-ILM hemorrhage were excluded, as well as cases that had any prior history of other diseases of the retina, choroid, or optic nerve.

Ophthalmic examinations

All patients had comprehensive ophthalmologic examinations before and after surgery. The comprehensive examinations included measurement of BCVA with refraction using a 5-m Landolt C acuity chart as well as indirect and contact lens slit-lamp biomicroscopy.

Color fundus photograph and swept source OCT imaging

All eyes were examined before surgery and at 1 month and 6 months after surgery by use of fundus photography (TRC 50DX; Topcon, Tokyo, Japan) and SS-OCT (DRIOCT-1 Atlantis, TOPCON Corporation, Tokyo, Japan). The fundus photographs and B-scan images were recorded on the same day as the clinical examinations for all patients. Analyses of color fundus photographs and B-scan images were performed by three retinal specialists (S.D., S.K., and Y.M.).

Main outcome measures

The main outcome measures were the localization of the hemorrhage and its effect on both pre and postoperative BCVA, central retinal thickness (CRT), continuity of the ellipsoid zone (EZ), and development of macular hole (MH).

Surgical technique

Displacement of SMH was performed according to previous reports.[20,21] Briefly, for phakic eyes, phacoemulsification with implantation of an intraocular lens was performed. After 25-gauge microincision vitrectomy, 4000 IU t-PA (GRTPA; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) in 0.1 mL was injected into the retina using a 38-gauge subretinal infusion needle (MedOne, Sarasota, FL) to liquefy the SMH. Intraoperative photocoagulation was applied to treat the RAM. In cases with sub-ILM hemorrhage, the hemorrhage was removed after removal of the ILM. ILM peeling was performed for cases with MH. Before finishing the surgery, we performed fluid-air exchange. In cases with MH, we also used air- 20% sulfur hexafluoride before finishing the surgery. Patients were instructed to maintain a facedown position for 3 days after the surgery. In cases with MH, patients maintained a facedown position until the closure of MH was confirmed by SS-OCT.

Statistics

BCVA was recorded as decimal values and converted to logarithm of the minimum angle of resolution (logMAR) units for statistical analysis. Visual acuity results are presented as logMAR units and Snellen visual acuities. Improvements in BCVA are shown using Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores. Data are presented as means ± standard deviations (SD). To evaluate the surgical outcomes, preoperative and postoperative BCVA values were compared using a one-way ANOVA with a Bonferroni correction. Other quantitative data were analyzed by using an unpaired t test, and categorical data were analyzed using Fisher's exact test. Probability values below 0.05 were considered significant. All statistical analyses were performed using Statistical Package for the Social Sciences software (SPSS, version 22.0; IBM Corporation, Armonk, N.Y., USA).

Results

Presence of preoperative macular intraretinal hemorrhage in SMH caused by RAM rupture

We analyzed preoperative SS-OCT B-scan images of SMH caused by RAM rupture and observed the presence of macular intraretinal hemorrhage (IRH) in 17/23 eyes (73.9%). Figure 1 shows a representative color fundus photograph and a B-scan image. In the SS-OCT B-scan images, macular IRH was detected in the outer plexiform layer (OPL) around the macula but not in the other retinal layers (nerve fiber layer, inner nuclear layer, outer nuclear layer).

Relationship between preoperative macular IRH and patient characteristics

Table 1 shows the associations between preoperative patient characteristics and the presence or absence of preoperative macular IRH. We divided all cases into two groups according to the presence or absence of IRH observed by preoperative B-scan imaging: an IRH (+) group and an IRH (-) group. In the preoperative B-scan images, we defined the distance from the ILM to the hemorrhage (DIH) as the shortest distance between the ILM and the SMH at the fovea (Figure 1, white arrows). The DIH was significantly shorter in the IRH (+) group than the IRH (-) group (42.2 ± 31.6 μm and 204.2 ± 90.0 μm, respectively, P = .014). In the 11 eyes (64.7%) classified as IRH (+), a radially spreading, fluff-like form (we called this the "fluffy sign") was observed (Table 1). By examining color fundus photographs and B-scan images, we found that the fluffy sign was formed by the margin of the IRH spreading from the macula to the periphery (Figure 1). The fluffy sign was not observed in the IRH (-) group. Regarding the presence of MH, there was no significant difference between the IRH (+) and the IRH (-) group (P = .124) (Table 1). Age, gender, disease duration, maximum diameter of the hemorrhagic lesion, maximum height of the SMH, and preoperative BCVA were not significantly different between the two groups (Table 1 and Figure 2).

Influence of preoperative macular IRH on visual function and retinal structure after displacement of SMH

Table 2 shows visual acuity and retinal structure data following displacement of SMH in both the IRH (+) group and the IRH (-) group. In the total patient group, BCVA was significantly improved from the time of surgery (1.34 ± 0.45, 20/438) to 1 month (0.84 ± 0.42, 20/138) and 6 months (0.72 ± 0.53, 20/105) after surgery (both P < .001). However, there was no significant improvement in BCVA between 1 month and 6 months after surgery (P = .112). In the IRH (+) group, BCVA was significantly improved from the time of surgery (1.36 ± 0.36, 20/458) to 1 month (0.98 ± 0.35, 20/191) and 6 months (0.89 ± 0.47, 20/155) after surgery (P = .006, P = .002, respectively; Figure 2). However, there was no significant improvement in BCVA between 1 month and 6 months after surgery (P = 1.000; Figure 2). In contrast, the IRH (-) group showed a significant improvement in BCVA not only at 1 month (P = .032) and 6 months (P = .013) after surgery, but also between 1 month and 6 months after surgery (P = 0.004; Figure 2). The improvement in BCVA at 6 months after surgery was significantly larger for the IRH (-) group (1.11 ± 0.55, 56 letters) than for the IRH (+) group (0.46 ± 0.44, 23 letters; P = .008; Figures 2 and 3). Regarding CRT and EZ continuity at 6 months after surgery, the IRH (+) group showed a significantly thinner CRT than the IRH (-) group (97.7 ± 53.5 μm and 173.0 ± 32.3 μm, respectively, P < .001) as well as a significantly higher appearance rate of discontinuous EZ (P = .002).

Influence of Development of MH on postoperative BCVA

We observed the preoperative or intraoperative development of MH in 7 out of the 23 eyes (30.4%) included in this study. At six months after surgery, cases with MH showed no significant difference in BCVA compared with cases without MH (0.90

± 0.46, 20/159, and 0.64 ± 0.55, 20/87, respectively; P=0.288). The MH was closed for the first surgery in 5 of the 7 eyes. In the remaining 2 eyes with open MH, expansion of the ILM peeling area and re-tamponade with gas were performed, and the MHs were successfully closed.

Representative cases from the IRH (+) group and the IRH (-) group are shown in Figures 4 and 5.

Discussion

In this study, we found that IRH existed in 73.9% of cases of SMH caused by RAM rupture. Using SS-OCT, we also observed that IRH was localized at the OPL around the macula. Previous studies have reported that retinal hemorrhage after RAM rupture can localize to the intraretinal space.[1,6,7,22] However, to the best of our knowledge, this report is the first to confirm the existence of macular IRH *in vivo* using SS-OCT. We also found that the postoperative BCVA of the IRH (+) group was significantly worse than that of the IRH (-) group, despite the successful displacement of SMH (Table 2). This indicates that preoperative IRH is a novel poor prognostic factor for SMH cases due to RAM rupture.

In the IRH (+) group, the postoperative CRT was significantly thinner and the EZ was more discontinuous than in the IRH (-) group (Figure 4 and Table 2). These results suggest that the photoreceptor cells of the macula were severely damaged in the IRH(+) group. There are two possible pathological conditions that may have led to photoreceptor cell damage. The first is the mechanical pressure caused by the subretinal hemorrhage. Both the postoperative CRT and the preoperative DIH were significantly thinner in the IRH (+) group than in the IRH (-)

group (Table 1). Furthermore, the EZ was more discontinuous preoperatively and the SRH tended to form a steep ridge at the fovea in the IRH (+) group (Figure 4). These results indicate that mechanical pressure from SRH can be high enough to cause photoreceptor cell death and thinning of the sensory retina. The second pathological condition that may have led to photoreceptor cell damage is the heavy exposure of photoreceptor cells to blood. The IRH (+) group showed the presence of both SRH and IRH, and it is therefore reasonable to assume that the photoreceptor cells were exposed to blood from both sides of the subretinal space and the OPL. It has been reported that blood is toxic to photoreceptor cells because it contains iron, which causes oxidative stress,[25,26,27] as well as fibrin and fibrin degradation products.[28,29,30]

There are two possible mechanisms that explain how blood from the RAM rupture becomes localized in the intraretinal space (Figures 6 and 7). The first mechanism is that the difference in biophysical properties between the sensory retina and the ILM, especially the difference in longitudinal elasticity, causes the blood from the ruptured RAM to flow into the intraretinal space (OPL) via the subretinal space (Figure 6). It has been reported that the longitudinal elasticity, that is Young's modulus, of the ILM is 3,000 to 30,000 times greater than that of the sensory retina.[31,32] Therefore, if the pressure in the subretinal space becomes high enough to penetrate the sensory retina at the fovea but not high enough to penetrate the ILM, the blood would flow into the intraretinal space. The second mechanism is that blood from the ruptured RAM flows directly into the intraretinal space (OPL) and then the subretinal hemorrhage pushes the intraretinal hemorrhage out to the peripheral retina (Figure 7). In this mechanism, gentle bleeding or oozing from the RAM at the intraretinal space would precede any vigorous subretinal bleeding. In contrast to the first mechanism, subretinal bleeding by this mechanism would not necessarily penetrate the outer layer of the fovea.

In this study, we also found that 64.7% of cases with IRH showed a characteristic radially spreading fluffy form, which we named the fluffy sign (Figures 1, 4, 6 and 7, Table 1). One possible mechanism that may explain the fluffy sign is that it forms when the axons of either neuronal cells or Muller cells obstruct the blood as it spreads to the peripheral retina within the OPL, resulting in different moving distances for the blood. The fluffy sign has clinical significance due to its ability to suggest the presence of IRH without the need for SS-OCT. However, the fluffy sign was not observed in all cases with IRH. Based on our observations, it is difficult to recognize the fluffy sign in situations in which the IRH boundary is hidden by preretinal or sub-ILM bleeding or in which the IRH boundary overlaps with the SMH boundary.

This study is limited by its retrospective nature, its small sample size, a relatively short follow-up period, the effect of simultaneous cataract surgery, and a lack of comparison with other surgical procedures for the displacement of SMH, such as intravitreal gas injection with or without t-PA injection[33-34,13,35,36 37] and vitrectomy with intravitreal injection of both t-PA and gas.[15,38] Nevertheless, our results indicate that the presence of IRH may be an effective poor prognostic factor for SMH associated with RAM rupture. A prospective clinical study involving a large number of patients and comparison with other surgical procedures is needed to confirm these results.

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