다수의 망막원공을 동반한 환자의 망막주변부 광각형광안저촬영양상

Ultra-widefield Fluorescein Angiography Findings in Patients with Multiple Retinal Holes

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Purpose: To evaluate ultra-widefield fluorescein angiography (UWFA) findings in patients with multiple retinal holes.

Methods: UWFA findings were compared between 73 eyes with more than two retinal holes and 39 age-matched controls. Factors associated with a high score were evaluated.

Results: Patients with multiple retinal holes showed a significantly higher prevalence of abnormal UWFA findings, such as Angiography Scoring for Uveitis Working Group (ASUWG) retinal vascular staining/leakage and capillary leakage at the posterior pole, and peripheral capillary leakage ($p < 0.001$ for all). Univariate analysis revealed that spherical equivalent ($r = -0.336$, $p = 0.005$) and number of retinal holes ($r = 0.267$, $p = 0.023$) were associated with a higher ASUWG score. Multivariate regression analysis revealed that the spherical equivalent was independently associated with a higher ASUWG score ($r^2 = 0.113$, $p = 0.005$). Vitreous tractions were detected by optical coherence tomography on the edge of retinal holes in these patients.

Conclusions: Eyes with strong focal adhesion between the vitreous cortex and the inner retinal surface could develop dye leakages and multiple retinal holes.

Keywords: High myopia; Retinal hole; Rhegmatogenous retinal detachment; Ultra-wide-field fluorescein angiography; Vitreoretinal adhesion

Introduction

Rhegmatogenous retinal detachment (RRD) is a potentially devastating condition that arises from posterior vitreous detachment (PVD) and retinal breaks [1,2]. Retinal breaks are classified into retinal tears or holes according to morphology

and relationship with the vitreous [3]. Retinal tears develop when there is a strong attachment of the retina to the vitreous, producing traction on susceptible areas of the retina during separation of the vitreous from the retina, eventually causing RRD when the fluid enters the subretinal space through the tears. However, the association between retinal

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Received: 2020. 5. 11.

Revised: 2020. 6. 5.

Accepted: 2020. 6. 5.

holes and PVD has not been clearly elucidated. Retinal holes are not usually associated with visible vitreous traction, and retinal hole-associated RRDs may exist without any obvious PVD [4,5]. Although some forms of viral retinitis, such as acute retinal necrosis and cytomegalovirus retinitis, have reportedly resulted in multiple retinal holes at the junction between a normal and a necrotic retina [6], there are limited data on the cause of retinal holes in eyes without retinal inflammation.

We hypothesized that patients with multiple retinal holes might have undiagnosed peripheral retinal pathology that might not easily be detected by conventional methods. The use of ultra-widefield fluorescein angiography (UWFA) has enabled better understanding of the pathological features of various peripheral retinal diseases [7,8]. We speculated that UWFA imaging would help facilitate an understanding of the pathophysiology of multiple retinal holes. In this study, therefore, we evaluated the UWFA findings of patients with multiple retinal holes and compared them with those of normal controls.

Materials and Methods

The case group in this retrospective study comprised patients who visited Keye Eye Center for multiple retinal holes from April 2018 to April 2019. The control group consisted of the eyes of patients who visited the same institution with central serous chorioretinopathy and branch retinal vein occlusion over the same period. Institutional Review Board (IRB)/Ethics Committee approval was obtained for the study (IRB no. P01-201908-21-011). The study protocol adhered to the principles of the Declaration of Helsinki.

Diagnosis of a retinal hole was made by the physician performing the fundus examination, when a retinal break was round-shaped and not associated with vitreoretinal traction [3]. The exclusion criteria were as follows: 1) history of other retinal diseases, such as age-related macular degeneration or diabetic retinopathy, 2) media opacity that markedly obscured the image on optical coherence tomography (OCT) or UWFA, 3) history of intraocular surgery including cataract surgery, 4) ocular trauma, 5) presence of intraocular inflammatory changes at presentation or history of uveitis, and 6) systemic diseases, such as hypertension or diabetes.

Comprehensive ocular examinations were performed,

including best-corrected visual acuity (BCVA), intraocular pressure (IOP) measurement, slit-lamp examination, refractive error, ultra-widefield fundus photography, OCT scanning using Spectralis Spectral Domain OCT version 5 (Heidelberg Engineering, Heidelberg, Germany), and UWFA (Optos Optomap Panoramic 200A Imaging System; Optos plc., Dunfermline, Scotland). OCT was scanned at the site of retinal tears, while patients were directed to look to the temporal or nasal side. UWFA images were obtained after intravenous injection of 10% fluorescein (Fluorescein 10%; Alcon, Fort Worth, TX, USA). UWFA images were evaluated according to the original scoring system suggested by the Angiography Scoring for Uveitis Working Group (ASUWG) [9]. The following findings were recorded: optic disc hyperfluorescence detected at 5-10 minutes, macular edema at 10 minutes, retinal vascular staining or leakage, capillary leakage at the posterior pole or periphery, retinal capillary nonperfusion, neovascularization, pinpoint leakage, and retinal staining or subretinal pooling at 5-10 minutes (Fig. 1). Two investigators measured the UWFA parameters; when the results were discordant, a third investigator was invited to give an additional opinion. All investigators were blinded to the clinical data and undertook the scoring independently.

Figure 1. Representative images of enrolled patients who showed positive results on ultra-widefield fluorescein angiography imaging. Peripheral retinal vascular leakages (A: arrowheads), peripheral capillary staining or leakages (B: circles), optic disc staining (C: arrows), and posterior pole capillary leakages (D: circles) are seen.

Statistical analysis

IBM SPSS Statistics software Version 15.0 (IBM Corp., Armonk, New York, NY, USA) was used for statistical analysis. Descriptive data were recorded as mean $\pm$ standard deviation unless otherwise specified. Chi-square and two-tailed *t*-tests were used to assess the differences between patients with and without multiple retinal holes. To better understand the association between clinical data and presence of retinal vascular leakage, we performed additional analysis of the ASUWG scores. The Shapiro-Wilk test was used to assess normality. The Pearson's correlation coefficient or Spearman rank correlation coefficient was determined to assess the association between continuous variables, according to the normality of distribution. Independent variables significantly associated with ASUWG scores in univariate analysis ($p < 0.05$) and potentially confounding parameters were included as independent covariables in a multivariate analysis by multiple regression analysis. A p value < 0.05 was considered statistically significant.

Results

The medical records of a total of 73 eyes with multiple retinal

holes and 39 control eyes were reviewed. The baseline demographics are summarized in Table 1. The groups were well matched in terms of age, sex, and refractive status. There was no significant difference in mean logMAR BCVA ($p = 0.220$) or IOP ($p = 0.122$). The mean refractive error was -5.20 ± 3.21 diopters in the case group and -4.60 ± 2.69 in the control group ($p < 0.001$). The mean number of retinal holes per eye was 3.10 ± 1.31 (range, 2-9) in the study group.

UWFA detected optic disc hyperfluorescence in seven of 73 eyes (9.6%) in the case group and two of 39 eyes (5.1%) in the control group ($p = 0.285$). Retinal vascular staining/leakage and capillary leakage at the posterior pole were found in 27 eyes (36.9%) and 11 eyes (15.1%), respectively, in the case group; while no eye in the control group showed retinal vascular staining/leakage or capillary leakage at the posterior pole ($p < 0.001$, for each). Peripheral capillary leakage was detected in 55 eyes (75.3%) in the case group and in four eyes (10.3%) in the control group ($p < 0.001$). No eye showed macular edema, retinal capillary nonperfusion, neovascularization, retinal staining, or subretinal pooling. Capillary leakages were detected at every retinal hole, while retinal vascular staining/leakages were detected at 18.4% of the retinal holes.

To evaluate the factors associated with severity of angio-

Table 1. Demographic characteristics and angiographic findings of enrolled patients

Characteristic	Multiple retinal hole group (n = 73)	Control group (n = 39)	<i>p</i> -value
Age (years)	39.8 $\pm$ 15.1	43.6 $\pm$ 10.9	0.753*
Sex (male)	30 (41.1)	17 (43.6)	0.477 [†]
BCVA (logMAR)	0.04 $\pm$ 0.09	0.01 $\pm$ 0.04	0.220*
Spherical equivalent (diopters)	-5.20 $\pm$ 3.21	-4.60 $\pm$ 2.69	<0.001*
Intraocular pressure (mmHg)	13.04 $\pm$ 2.80	13.94 $\pm$ 2.71	0.122*
Smoking	15 (20.5)	7 (17.9)	0.808 [†]
Retinal detachment (yes)	4 (5.4)	0	0.296 [†]
Angiographic findings (yes)			
Optic disc hyperfluorescence	7 (9.6)	2 (5.1)	0.285 [†]
Retinal vascular staining/leakage	27 (36.9)	0	<0.001 [†]
Capillary leakage at posterior pole	11 (15.1)	0	<0.001 [†]
Capillary leakage at periphery	55 (75.3)	4 (10.3)	<0.001 [†]
ASUWG score	3.98 $\pm$ 3.61	0.21 $\pm$ 0.61	<0.001 [†]

Values are presented as mean $\pm$ standard deviation or number (%).

logMAR = logarithm of minimal angle of resolution ; BCVA = best corrected visual acuity; ASUWG = Angiography Scoring for Uveitis Working Group.

**t*-tests; [†]Chi-square test.

graphic abnormalities in eyes with multiple retinal holes, we performed a regression analysis of ASUWG scores (Table 2). Univariate analysis revealed that spherical equivalent ($r = -0.336, p = 0.005$) and number of retinal holes ($r = 0.267, p = 0.023$) were associated with a higher ASUWG score. After adjustments for age and sex, multivariate regression analysis revealed that spherical equivalent was independently associated with a higher ASUWG score ($r^2 = 0.113, p = 0.005$; Fig. 2).

To evaluate the relationship between retinal hole and vitreous traction, we analyzed OCT images at the site of retinal holes from five eyes with OCT scans on the retinal holes. Every OCT scan of retinal holes found vitreous traction on the edge of the retinal hole, supporting the hypothesis of contribution of vitreous traction on development of a retinal hole (Fig. 3).

Figure 2. A scatter plot showing the correlation between refractive error and Angiography Scoring for Uveitis Working Group (ASUWG) score.

Fig. 4 shows a representative UWFA image of a patient with multiple retinal holes. The patient was a 21-year-old female referred for localized RRD with multiple retinal holes found in preoperative examination for refractive surgery. A fundus examination revealed a retinal hole-associated localized RRD in the superotemporal quadrant of her right eye, an atrophic hole without RRD in her left eye, but no vitreous traction on the atrophic holes in either eye. Neither eye showed obvious PVD. In addition, opaque discoloration was detected in the peripheral retina adjacent to the retinal holes

Figure 3. Serial optical coherence tomography (OCT) section of a retinal hole from a 27-year-old male patient. (A) Two retinal holes were detected on the superotemporal retina. Black lines; OCT sections for (B-D). (B) Vitreous traction (arrowheads) was detected superior to the retinal hole. (C) On the edge of the retinal hole, vitreous traction (arrowheads) and slight retinal detachment were found. (D) Inferior to the retinal holes, vitreous tractions (arrowheads) were detected in a bilateral direction.

Table 2. Factors associated with the high ASUWG score in patients with multiple retinal holes

Characteristic	Univariate analysis		Multivariate analysis	
	Regression coefficient	p-value	Regression coefficient	p-value
Age	-0.166	0.160	-0.134	0.333
Sex	-0.145	0.219	-0.084	0.512
Smoking	0.109	0.361	0.038	0.756
Spherical equivalent	-0.336	0.005	-0.403	0.005
Intraocular pressure	-0.122	0.344	-0.121	0.334
Number of retinal holes	0.267	0.023	0.225	0.034

ASUWG = Angiography Scoring for Uveitis Working Group.

Figure 4. Representative images of an 18-year-old female patient who was referred for asymptomatic rhegmatogenous retinal detachment (RRD) in her right eye and bilateral multiple retinal holes that were detected during screening examination for refractive surgery. (A) The right eye showed focal retinal detachment at the supero-temporal retina with multiple holes (black arrowheads) and discoloration at the infero-temporal retina (blank arrowheads). (B) A retinal hole at the temporal retina (arrow) and retinal discoloration (blank arrowheads) were detected in the extension of the retinal hole detected in her left eye. (C, D) Ultra-widefield fluorescein angiography (UWFA) showed bilateral peripheral retinal vascular leakages and peripheral capillary leakages, which included the area of RRD and the retinal hole. Yellow arrowheads and arrow; Same areas for black arrowheads and arrow in (B). (E, F) Barrier LASER photocoagulation was performed to prevent progression of RRD in both eyes. White line; OCT section for (G). (G) OCT imaging of the peripheral retina showed adhesion of the vitreous cortex (blank arrows) on the peripheral retinal surface adjacent to the retinal hole.

in both eyes. An OCT image of the discolored retina showed adhesion of the vitreous cortex to the peripheral retinal surface adjacent to the retinal hole. UWFA showed perivascular

leakages in the peripheral retina, with extent in accord with the opaque discoloration.

Discussion

Although RRD is a vision-threatening condition, the pathogenesis of retinal break, which is the most important determinant for RRD, is not fully understood. It is commonly believed that the mechanism involves a vitreoretinal adhesion associated with PVD, which frequently results in retinal tears. However, the pathophysiology of focal retinal thinning or atrophy leading to a retinal hole is largely unknown.

We found in this study that patients with multiple retinal holes showed profound vascular or capillary leakages at the periphery, and the leakages were more profound in myopic eyes. Retinal vascular or capillary leakages can be caused by various retinal conditions, such as increased venous pressure from vascular occlusion, vascular endothelial cell damage from diabetes [10], increased inflammatory cytokines from uveitis [11], and mechanical traction from vitreoretinal interface abnormalities [12]. In the data, no eye with multiple retinal holes showed retinal vascular occlusion, diabetic retinopathy, or uveitis. Therefore, we speculated that focal adhesion of the vitreous cortex might play a role in the vascular or capillary leakages seen in our patients, as detected in the OCT scan.

Takahashi et al. [13] reported cases with multiple PVD with the posterior vitreous adhered to the inner retinal surface of multiple points in myopic eyes. It is generally accepted that myopic eyes tend to have vitreoretinal interface abnormalities resulting from abnormal coordination between the eye's relatively rigid inner structures and progressively elongated sclera [14,15]. Well-known vitreoretinal interface abnormalities include epiretinal membranes, retinoschisis, lamellar holes, and paravascular retinal cysts, as most studies focus on the foveal area [16-19]. Scleral elongation can occur at the posterior pole, as well as equatorially [20]. A patient with equatorial-type myopia would manifest vitreoretinal interface abnormalities in the peripheral retina. We speculated that eyes with strong focal adhesions between vitreous cortex and inner retinal surface could develop dye leakages and multiple retinal holes as the eyeball elongated, as evidenced by the OCT scan shown in Fig. 3.

The present study has several limitations. First, we includ-

ed patients with central serous chorioretinopathy and branch retinal vein occlusion in the control group, which might have influenced study outcomes. Second, we could not compare the findings between holes and tears since we only included eyes with retinal holes. We speculated that acute PVD at the focal adhesive lesion would progress to retinal tear, while chronic irritation from incomplete PVD would progress to retinal hole. Further study is warranted to evaluate the difference in vitreoretinal interface between eyes with retinal holes and tears. Third, it was difficult to obtain detailed information about the vitreoretinal interface of the peripheral retina in eyes with clear vitreous. Further study to obtain more detailed information about temporal changes in the peripheral vitreoretinal interface is warranted to confirm study findings.

Conflicts of Interest

The authors declare no conflicts of interest relevant to this article.

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