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RETINAL DISORDERS

Evolution and visual outcomes of outer foveolar lucency after surgery for large idiopathic macular hole

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Abstract

Purpose To explore the evolution of outer foveolar lucency (OFL) after vitrectomy and the correlation between OFL and visual acuity (VA) outcome in eyes with large idiopathic macular hole (IMH).

Methods In this retrospective study, 244 eyes of 233 subjects with large IMH (diameter > 400 μm), who underwent vitrectomy, were included. Preoperative clinical data, postoperative optical coherence tomography (OCT) images, and VA at 1-, 4-, and 10-month visits were documented. The prevalence, incidence, and width of OFL and their correlation with postoperative VA were analyzed.

Results The prevalence of OFL was 10.4% (24/231) at 1 month and significantly increased to 30.4% (55/181) at 4 months ($P < 0.001$) and 34.2% (25/73) at 10 months ($P < 0.001$). The incidence was 26.1% (40/153) and 22.0% (9/41) at 4 and 10 months, respectively. OFL appeared at 1 month while disappeared at 4 or 10 months in 8 eyes (50.0%). The presence of OFL at 1 month was negatively associated with IMH diameter (Nagelkerke $R^2 = 0.06$; $P = 0.02$). Eyes with OFL at 4 months had better VA at their 4-month visit than eyes without OFL ($P = 0.02$). Eyes with early-developed OFLs had better VA at 10 months than those with later-developed ones ($P = 0.02$). Width of OFL was not associated with postoperative VA at any point.

Conclusions OFL is not rare in eyes with large IMH after surgery. It can occur gradually and remain during the 10-month follow-up. The presence of OFL appears to have no negative impact on the postoperative VA and it may represent the remodeling of foveal photoreceptors.

Keywords Idiopathic macular hole · Outer foveolar lucency · Prevalence · Incidence · Visual acuity · Optical coherence tomography

Introduction

Vitrectomy combined with intravitreal gas tamponade has been verified as effective to close idiopathic macular holes (IMH) [1, 2] and contributes to both anatomical restoration and functional improvement [3]. Optical coherence tomography (OCT) displays the retinal microstructure clearly and has become the primary imaging method for diagnosing IMH and confirming anatomical success after IMH surgery.

Outer foveolar lucency (OFL) is commonly found during the restoration of the fovea after MH surgery [4] and has gained a lot of attention by researchers in recent years. There are various terms of OFL in previous studies, such as outer foveal defect [5–9], subretinal fluid [5, 10, 11] or space [12], outer retinal cysts [7, 13–15], foveal detachment [6, 14], bridge formation [5, 16], outer retinal elevation [17], and foveolar lucency [4, 18, 19]. However, the definition of OFL has not reached an agreement on whether OFL includes the disruption of the photoreceptor inner and outer segment (IS/OS) junction or not. The evolution of OFL was described inconsistently in previous studies. It was reported that the prevalence of OFL decreased over time [11, 17–19], but Kawano and associates [7] found it remained stable during the 12-month follow-up. In addition, previous studies indicated that the presence of OFL was not

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associated with postoperative visual acuity (VA) [8, 10, 15, 18, 19], and the impact of width of OFL on postoperative VA still remains controversial [10, 11, 18]. Moreover, most of these researches only focused on eyes with small to medium IMH. The correlation between OFL and postoperative VA in eyes with large IMH still remains unclear. The current study is being conducted to explore the evolution of OFL and investigate the correlation between both the presence and width of OFL and the postoperative VA in a large cohort of eyes with large MHs. This study may help explain the mechanism of IMH closure after surgery.

Methods

Patients and materials

This retrospective study included patients with large IMH (diameter > 400 μm, stage 3 or 4 based on Gass's classification system in 1995 [20]), who underwent 23-gauge vitrectomy and obtained successful macular hole (MH) closure in Beijing Tongren Hospital from July 2015 to January 2019. IMH was diagnosed based on clinical data, fundus examination, OCT images, and intraoperative observation. Exclusion criteria included eyes with IMH diameter equal or less than 400 μm, high myopia, previous vitrectomy, uveitis or other vitreoretinal diseases, and history of intravitreal injection. This study adhered to the Helsinki declaration and its later amendments, and the whole protocol was approved by the ethical review committee of Beijing Tongren Hospital, Capital Medical University. All the participants signed written informed consents after exhaustive explanation of the surgery.

Clinical and demographic data

Preoperative clinical and demographic data including age, gender, affected eye, and the stage and diameter of MH were collected from medical records. The stage and diameter of the MH were analyzed on OCT images (Cirrus high-definition OCT; Carl Zeiss, Dublin, CA). OFL was defined as a hyporeflective, rectangular area in the outer fovea with a width over 50 μm, which laid below the external limiting membrane (ELM) and above the retinal pigment epithelium (RPE) (Fig. 1). Eyes in which lucency appeared in the region of foveola, on any alignment of horizontal or vertical OCT images, were categorized into the "with-OFL" group. The width of OFL was defined as the maximum diameter of OFL among all alignments of the horizontal OCT images. Any hyporeflective space in the outer fovea with irregular shape and continuous IS/OS line or signal near either ELM or RPE was not considered as OFL in this study. Eyes with this kind of space postoperatively were excluded in further analysis. Follow-up with patients occurred at 1, 4, and 10 months after surgery. The postoperative clinical data collected at each visit included the prevalence, incidence, and width of OFL and postoperative best-corrected visual acuity (BCVA).

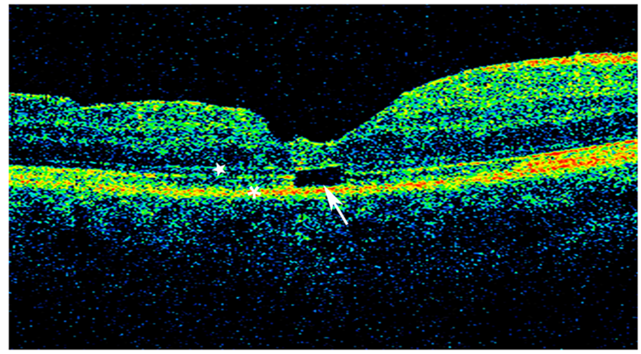

Fig. 1 Representative optical coherence tomography image (OCT) of outer foveolar lucency. The postoperative OCT image shows a rectangular outer foveolar lucency (arrow) lying below the external limiting membrane (five-pointed star) and above the retinal pigment epithelium (asterisk)

Surgical procedures

All the patients underwent 23-gauge standard three-port pars plana vitrectomy combined with internal limiting membrane (ILM) peeling by a single surgeon (W.L.). If necessary, phacoemulsification, intraocular lens implantation, and induction of posterior vitreous detachment were performed. Any epiretinal membrane present was peeled by intraocular forceps. The ILM was peeled over a circular area with a diameter of two to three optic disk diameters centered in the MH without prior staining. Before July 2016, fluid-air exchange was performed with either 14% hexafluoroethane (C_2F_6) or 12% octafluoropropane (C_3F_8) gas to keep the intraocular pressure around 20 mmHg. After July 2016, due to the unavailability of gas, sterile air was retained in vitreous cavity instead and the intraocular pressure was kept around 25 mmHg. Transscleral suture was applied if there was air or gas leakage. All patients were asked to keep strict face-down position for 1 week (for air) or 2 weeks (for gas) after surgery along with routine postoperative pharmaceutical therapy.

Statistical analysis

All statistical analysis was performed using SPSS Statistics, v 25.0 (IBM, Chicago, IL). A P value equal or less than 0.05 was considered statistically significant. BCVA was converted to the logarithm of the minimum angle of resolution (LogMAR). Continuous variables like age, BCVA, MH diameter, and width of OFL were presented as mean ± standard deviation (SD) and were analyzed using Mann-Whitney U test. Fisher's exact test was carried out for categorical variables like gender and affected eye, which were presented as proportions. Eyes were classified into "with-OFL" group and "without-OFL" group at each follow-up. Multivariate linear regression was used for factors of postoperative VA at each visit. The correlation between width of OFL and postoperative VA was analyzed using univariate linear regression.

Results

Clinical demographics and prevalence of outer foveolar lucency

Two hundred and forty-four eyes of 233 patients (49 men, 21.0% and 184 women, 79.0%) were recruited in this study, including 113 right eyes (46.3%) and 131 left eyes (53.7%). The mean age, preoperative macular hole diameter, and postoperative follow-up period was 64.5 ± 5.1 years (range, 48 to 84 years), 598.1 ± 116.6 μm (range, 400 to 909 μm), and 10.2 ± 9.6 months (range, 1 to 40 months), respectively.

OFL was identified in 10.4% (24/231), 30.4% (55/181), and 34.2% (25/73) of eyes at 1, 4, and 10 months after surgery, respectively. The prevalence of OFL at 4 months ($P < 0.001$) and 10 months ($P < 0.001$) were both significantly higher than that at 1 month. No significant difference was found in the prevalence of OFL between eyes with gas and air tamponade at 1 month (10.3%, 8/78 vs 10.5%, 16/153; $P = 1.00$), 4 months (34.4%, 21/61 vs 28.3%, 34/120; $P = 0.49$), and 10 months (45.5%, 10/22 vs 29.4%, 15/51; $P = 0.28$).

Evolution of outer foveolar lucency

In this study, 169 eyes met the criterion of attending at least the 1- and 4-month follow-ups. They were divided into two groups: eyes attending 1- and 4-month follow-ups only (group A, $N = 104$) and eyes attending 1-, 4-, and 10-month follow-ups (group B, $N = 65$). The evolution of OFL in the two groups during the 10-month follow-up is shown in Table 1. OFL was absent in 96 eyes and 57 eyes at 1 month in group A and group B, respectively. Among these eyes, OFL occurred in 24 eyes (25.0%) in group A and 16 eyes (28.1%) in group B at 4 months. Thus, in total, OFL occurred in 40 eyes (26.1%, 40/153) at 4 months. In group B, OFL was absent in 41 eyes at both 1 and 4 months while it occurred in 9 eyes (22.0%) at 10 months. OFL appeared at 1 month while disappeared at 4 or 10 months in 8 eyes (50.0%, 8/16, Fig. 2). A case indicating the OFL occurrence till 10 months is shown in Fig. 3.

Correlation between outer foveolar lucency and postoperative visual acuity

Before analyzing the correlation between OFL and postoperative VA, potential factors associated with both OFL and VA (age, gender, affected eye, and MH diameter) were explored. Regression analysis showed that preoperative MH diameter was the only factor affecting both OFL and VA: MH diameter negatively correlated with the presence of OFL at 1 month (Nagelkerke $R^2 = 0.06$; $P = 0.02$), postoperative VA at 1 month ($R^2 = 0.11$; $P < 0.001$), VA at 4 months ($R^2 = 0.11$; $P < 0.001$), and VA at 10 months ($R^2 = 0.07$; $P = 0.02$). Therefore, covariance analysis was used to eliminate the confounding effect of preoperative MH diameter. VA between with-OFL group and without-OFL group at each follow-up was compared. Covariance analysis indicated that eyes with OFL at 4 months had better VA at their 4-month visit than eyes without OFL (LogMAR VA 0.31 ± 0.32 vs 0.43 ± 0.34; $P = 0.02$). There was no significant difference in VA at 1 and 10 months between eyes with and without OFL at 1 and 10 months, respectively (LogMAR VA 0.37 ± 0.23 vs 0.57 ± 0.38; $P = 0.11$; LogMAR VA 0.20 ± 0.19 vs 0.27 ± 0.24; $P = 0.28$, respectively).

Multivariate linear regression analysis suggested that VA at 1 month negatively correlated with MH diameter ($R^2 = 0.11$; $P < 0.001$; Table 2); VA at 4 months was associated with the presence of OFL at 4 months (positively, $R^2 = 0.15$; $P = 0.004$) and the MH diameter (negatively, $R^2 = 0.15$; $P < 0.001$); VA at 10 months did not correlate with age, affected eye, gender, and MH diameter or the presence of OFL at 1, 4, or 10 months.

Eyes with early-developed OFLs (occurred at 1 month) had better VA at 10 months than eyes with later-developed OFLs (did not occur until 4 or 10 months, LogMAR VA 0.10 ± 0.09 vs 0.25 ± 0.22, N 9 vs 22; $P = 0.02$). No significant difference in MH diameter was found between eyes with early- and later-developed OFLs (533.78 ± 112.11 μm vs 619.40 ± 140.46 μm, N 23 vs 49; $P = 0.15$).

Table 1 The evolution of outer foveolar lucency during the 10-month follow-up

Groups	Status of OFL			Number of eyes
	1 month	4 months	10 months	
Group A	+	+		5
	+	−		3
	−	+		24
	−	−		72
Group B	+	+	+	3
	+	+	−	1
	+	−	−	4
	−	+	+	10
	−	−	+	9
	−	+	−	6
	−	−	−	32

OFL outer foveolar lucency

+: with outer foveolar lucency, −: without outer foveolar lucency

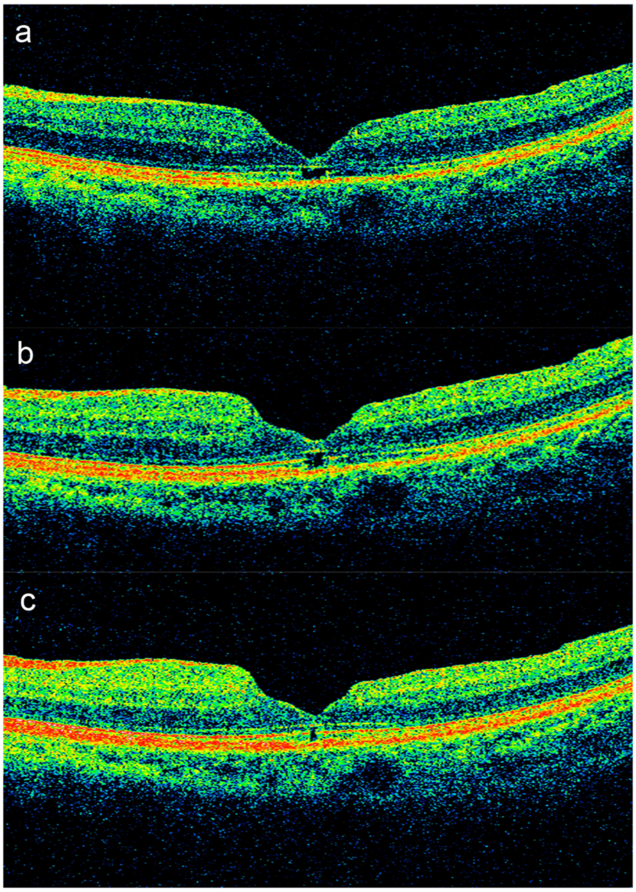

Fig. 2 Postoperative optical coherence tomography (OCT) images of a 61-year-old woman in the left eye. The preoperative macular hole diameter is 534 μm. **a** The postoperative 1-month OCT demonstrates an outer foveolar lucency with a width of 153 μm. The LogMAR visual acuity is 0.2. **b** The postoperative 4-month OCT shows an outer foveolar lucency with a decreased width of 66 μm. The LogMAR visual acuity is 0.2. **c** A hyporeflective area is noted in OCT obtained at 10-month visit with a width much smaller than 50 μm. The LogMAR visual acuity is 0.1

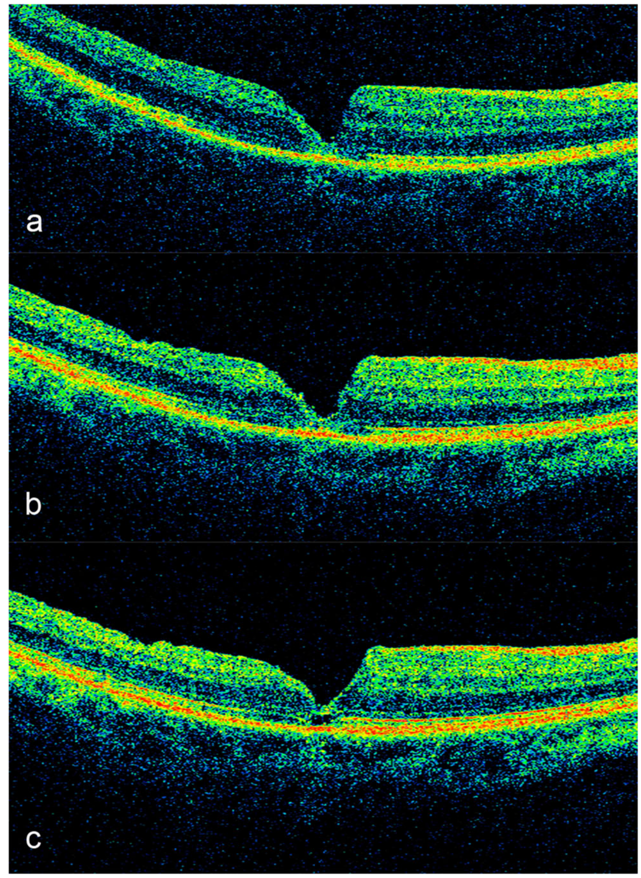

Fig. 3 Postoperative optical coherence tomography (OCT) images of a 65-year-old woman after successful macular hole surgery in the right eye. The preoperative macular hole diameter is 627 μm. **a**, **b** Anatomic macular hole closure is noted in OCT obtained at 1- and 4-month visits. The LogMAR visual acuity is 0.2 at both 1- and 4-month visits. **c** An approximately rectangular lucency appears on the same alignment of OCT obtained at 10 months, which is 142 μm wide. The LogMAR visual acuity is 0.1

Width of outer foveolar lucency and its effect on postoperative visual acuity

The mean width of OFL was 185.3 ± 91.5 μm (range, 56 to 422 μm), 182.3 ± 98.4 μm (range, 56 to 524 μm), and 174.4 ± 80.0 μm (range, 65 to 417 μm) at 1, 4, and 10 months respectively. There was a trend that the width decreased over time, but no significant difference was found between width at 1-, 4-, and 10-month visits ($P = 0.83$; Fig. 4).

Univariate analysis showed that the postoperative VA was not significantly correlated with the width of OFL at each time point during the 10-month follow-up. There was also no significant difference in VA between eyes with large OFL (width larger than its median) or small OFL (width smaller than its median) at any time point during follow-up.

Discussion

Previously, OFL was defined as any subfoveal hyporeflective space after MH surgery, with or without IS/OS junction disruption [7, 10, 11, 17, 19]. Also, the terms of OFL vary in different clinical reports [4–19]. This study focused on one type of lucency with a distinct area, specific shape, and absolute IS/OS junction disruption. These variables may explain why only 10.4% of eyes were identified with OFL at 1 month in the current study, while in previous studies the number was around 33.7 to 71.1% [7, 11, 18, 19]. In addition, due to the negative association between MH diameter and the presence of OFL at 1 month, the larger preoperative MH diameter in the current study might, to some extent, decrease the prevalence of OFL. Moreover, the larger sample size in this study might be another reason for the discrepancy.

In previous studies, the prevalence of OFL decreased over time [11, 12, 17–19]. Many researchers explained that MH closure began with the re-approximation of the

Table 2 Factors associated with visual acuity at each follow-up after surgery

Covariate	VA at 1 month, LogMAR		VA at 4 months, LogMAR		VA at 10 months, LogMAR	
	Standardized coefficient (β)	*P* value[a]	Standardized coefficient (β)	*P* value[a]	Standardized coefficient (β)	*P* value[a]
Age (years)	0.05	0.46	0.03	0.74	− 0.05	0.75
Affected eye	− 0.03	0.66	0.09	0.24	− 0.14	0.31
Gender	0.05	0.48	0.04	0.61	− 0.12	0.46
MH diameter (μm)	0.33	< 0.001*	0.32	< 0.001*	0.16	0.24
OFL at 1 month	− 0.10	0.11	− 0.08	0.31	− 0.17	0.22
OFL at 4 months	–	–	− 0.22	0.004*	0.02	0.92
OFL at 10 months	–	–	–	–	− 0.13	0.41

VA visual acuity, *LogMAR* logarithm of the minimum angle of resolution, *MH* macular hole, *OFL* outer foveolar lucency

[a] Multiple linear regression analysis

[*] Significant *P* values (< 0.05)

inner retina, which conduced to bridge formation over RPE, thus producing the OFL [4, 6, 8, 9, 12, 16, 17]. It was postulated that OFL resolved through photoreceptor regeneration [8], new glial cell proliferation [8, 9], or RPE pumping the vitreous fluid [4, 8]. In the present study, 8 eyes developed OFL during the early postoperative period and resolved over time, which was consistent with the results in previous studies and could be explained by these theories. However, at the 10-month visit, OFL was still present in over 1/3rd of the eyes. Moreover, in a considerable number of eyes, OFL occurred gradually and the incidence of OFL stayed relatively high at 4 and 10 months, leading to the significant higher prevalence of OFL at 4 and 10 months than that at 1 month. In the present study, these facts could not be explained by the hypothesis that OFL came from bridge formation of the inner retina during early postoperative period and resolved because of re-approximation of the tissue and resolution of subretinal fluid. Kawano and colleagues [7] reported that the prevalence of OFL remained relatively high at 1, 3, 6, and 12 months, but they did not offer an explanation why the lucency in their study did not resolve over time. They indicated that eyes with small MH, rather than large MH, were more likely to bridge the hole during

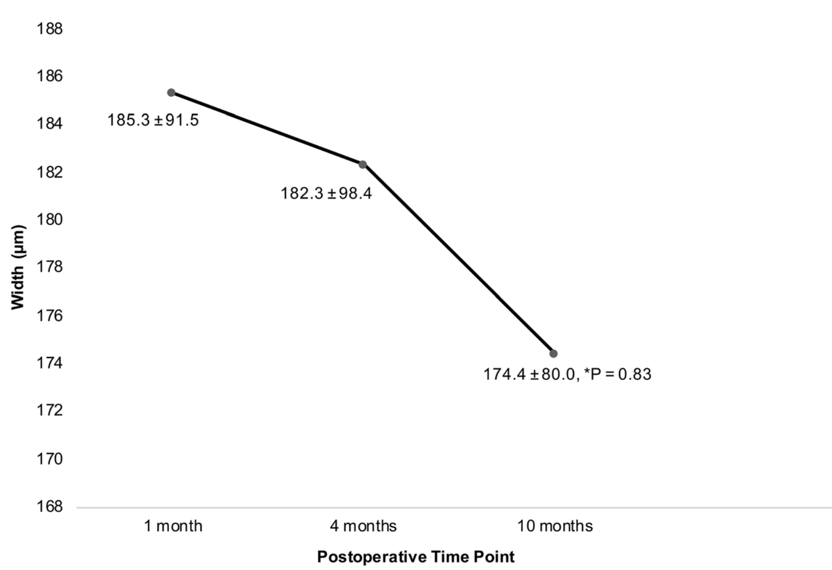

Fig. 4 The width of outer foveolar lucency at each follow-up. There is no significant difference between width at 1-, 4-, or 10-month visits (asterisk, $P = 0.83$)

early follow-up period. In the current study, we also found the tendency that eyes with smaller preoperative MH diameter tend to develop OFL at 1 month. Since the MHs in the current cohort were large, most OFLs occurred gradually and remained during the 10-month follow-up period. Only in a few eyes, OFL developed during early postoperative period and disappeared over time. We postulated that in eyes with large MH, the presence of OFL may represent the remodeling of foveal photoreceptors.

The correlation between OFL and postoperative VA was of major interest in previous studies. Some researchers indicated that the final VA was not associated with the presence of OFL [11]. They also found no significant difference in final BCVA [10], mean postoperative VA [15], or mean extent of vision improvement [10, 19] between eyes with and without OFL. Besides, Grewal and colleagues [18] compared postoperative VA at 1, 3, 6, and 12 months between eyes with and without OFL and found no significant difference. Kang and associates [8] reported that eyes with OFL had better VA at 1-, 3-, 6-, and 12-month visits than eyes without OFL, but they attributed it to the confounding effect of the preoperative MH diameter. However, most of the studies mentioned above only focused on the correlation between OFL examined at initial or 1-month visit and the postoperative VA. It remains unclear whether the presence of OFL at each follow-up has an effect on postoperative VA. In this study, with larger sample size and a focus on large MH, we found eyes with OFL at 4 months had better VA at their 4-month visit than eyes without OFL. Multivariate regression analysis also showed that the presence of OFL at 4 months positively correlated with VA at 4 months. The presence of OFL at 1 and 10 months were not associated with postoperative VA at 1 and 10 months, respectively. Besides, eyes with early-developed OFLs had better VA at 10 months than those with later-developed ones. Although the difference was not significant, it might be attributed to the tendency of the smaller MH diameter in eyes with early-developed OFLs. The relatively small sample size in eyes with early- or later-developed OFLs could possibly account for the reason why the comparison of MH diameter did not reach a statistical significance. The results of this study may also be explained by the hypothesis that the presence of OFL represents the remodeling of foveal photoreceptors so that patients with persistent or delayed occurring OFL can still obtain relatively good postoperative VA.

It remains unclear if the width of OFL influences the postoperative VA. Rahman and associates [10] indicated that the width of OFL 6 weeks after surgery was not associated with the final vision. Ehlers and colleagues [11] found that the absolute area of OFL did not significantly correlate with BCVA at any point. However, Grewal and associates [18] reported that the width of OFL at 1 month was negatively predictive of BCVA at 6 and 12 months. In this study, at no point during the 10-month follow-up, did we find a correlation between OFL width and postoperative VA, or a significant difference in postoperative VA between eyes with large or small OFL. Foveola is the central part of the fovea with a diameter of around 350 μm [21], where VA reaches its maximum [22]. In this study, OFL was located within the foveola with a much smaller mean diameter (170 to 180 μm). Thus, it could be assumed that OFL has no significant negative impact on the postoperative VA because remodeled foveal photoreceptors around the lucency contribute to the central vision.

During this study, gas was replaced by sterile air during surgery after July 2016 due to the unavailability of gas. Our previous study shows that air tamponade for large MH could provide a relatively satisfactory initial closure rate (89.6%) [23]. Here, we demonstrated that eyes with gas or air tamponade showed no significant difference in the prevalence of OFL at any follow-up. Thus, apart from gas, air could also be considered an effective tamponade agent for MH surgery.

There are some limitations in this study that should be acknowledged, including the fact that some patients did not attend every follow-up visit. When investigating the evolution of OFL, only eyes attending at least the 1- and 4-month follow-ups were included. Although the total number of eyes in groups A and B was smaller than that of eyes attending 1-month follow-up (169 vs 231), it was merely slightly lower than that of eyes attending 4-month follow-up (169 vs 181). This number is already much larger than other studies. Besides, the number of eyes in group B was also comparable to that of eyes attending 10-month follow-up (65 vs 73). Thus, the results based on data of groups A and B were relatively reliable with minimal selection bias. In addition, we did not include eyes with, to some extent, non-typical OFL: subfoveal hyporeflective space with irregular shape and continuous IS/OS line or signal either underneath the ELM or above the RPE. This reduced our sample size a bit, but it improved the definition consistency and internal comparability of our study population.

In conclusion, OFL is not rare in eyes with large IMH after surgery. It can occur gradually and remain during the 10-month follow-up. The presence of OFL appears to have no negative impact on the postoperative VA and it may represent the remodeling of foveal photoreceptors. The evolution and visual outcomes of OFL in eyes with large IMH have revealed new aspects with regard to the pathoanatomy and function after MH surgery. OFL may play a role in the restoration process of the outer retina.

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Code availability Not applicable.

Authors' contributions Conceptualization and methodology: Biying Qi, Yanping Yu, and Wu Liu. Material preparation, data collection, and analysis: Biying Qi. Writing—original draft preparation: Biying Qi. Writing—review and editing: Yanping Yu, Wu Liu, Qisheng You, and Biying Qi. Support of statistical techniques: Zengyi Wang, Jing Wang, and Lingzi Liu. Supervision and surgical support: Wu Liu. Approval of manuscript: all authors.

Availability of data and material All data relevant to the study are included in the article. The deidentified participant data are in the team's database, which is available only from the corresponding author. For reusing, please contact WL (wuliubj@sina.com) for permission.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the ethical review committee of Beijing Tongren Hospital, Capital Medical University.

Consent to participate Informed consent was obtained from all individual participants included in this study.

Consent to publish Patients signed informed consent regarding publishing their data and photographs.

Proprietary interests None.

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