Progression of lamellar hole-associated epiretinal proliferation and retinal changes during long-term follow-up

Denise Compera,[1] Ricarda G Schumann,[1] Matteo G Cereda,[2] Alessandra Acquistapace,[2] Viviane Lita,[1] Siegfried G Priglinger,[1] Giovanni Staurenghi,[2] Ferdinando Bottoni[2]

[1]Department of Ophthalmology, Ludwig-Maximilians-University, Munich, Germany
[2]Eye Clinic, Department of Biomedical and Clinical Science 'Luigi Sacco', Sacco Hospital, University of Milan, Via G.B. Grassi 74, Milan, Italy

Correspondence to
Dr Denise Compera, Ludwig-Maximilians-University, Department of Ophthalmology, Vitreoretinal Pathology Unit, Mathildenstrasse 8, 80336 Munich, Germany; denise.compera@med.uni-muenchen.de

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ABSTRACT

Purpose To report on progression of lamellar hole-associated epiretinal proliferation (LHEP) in eyes with lamellar macular holes (LMH) using spectral-domain optical coherence tomography (SD-OCT), and to correlate with intraretinal changes and visual function.

Methods From a retrospectively reviewed series of 167 eyes with non-full-thickness macular holes, we exclusively included a subgroup of 34 eyes with LMH and LHEP by SD-OCT evaluation. In these eyes, area of LHEP, intraretinal changes of defect diameter, central retinal thickness, defects of the ellipsoid zone and occurrence of a contractive epiretinal membrane were analysed. Additionally, clinical data were documented.

Results Area of LHEP significantly increased during a mean follow-up period of 40.5 months (median 52 months). Analysing intraretinal changes, a significant enlargement of minimum and maximum horizontal lamellar hole diameter was found that correlated with the area of LHEP. Defects of the ellipsoid zone were seen in 65% of the eyes at baseline and in 85% at the end of follow-up. Increase of maximum horizontal hole diameter and ellipsoid zone defects correlated with a decline of visual acuity. Fifty per cent of patients with LMH and LHEP also demonstrated extrafoveal typical contractive epiretinal membranes with retinal folds.

Conclusions Long-term follow-up revealed an increase of the area of LHEP in eyes with LMH that correlated with the enlargement of lamellar hole diameter and ellipsoid zone defects. Our data delineate the progression of intraretinal changes in association with a decline of visual function in this subgroup of LMH eyes.

INTRODUCTION

Lamellar hole-associated epiretinal proliferation (LHEP) was recently introduced to characterise a thick homogenous layer of moderately reflective material at the edge of lamellar macular holes (LMHs) by spectral-domain optical coherence tomography (SD-OCT).[1–9] In contrast to conventional epiretinal membranes of macular pseudoholes, LHEP does not show common signs of traction on retinal layers such as retinal folds.[7–9]

Immunocytochemical and ultrastructural studies reported on differences in cell composition of LHEP and conventional epiretinal membranes.[3 7 10] Whereas myofibroblasts with contractive properties are the predominant cell type in epiretinal membranes removed from macular pseudoholes, cells in LHEP mostly presented hyalocytes, fibroblasts and glial cells without contractive properties. LHEP consists of densely packed cell agglomeration on vitreous collagen strands as seen in electron microscopy. These findings point to the hypothesis that LHEP develops from vitreous.[7 10] On the other hand, immunoreactivity for antiglutamine synthetase in LHEP indicated that this atypical material on the retinal surface might be a Müller cell-driven process originating from inner retinal layers of the macular defect.[8 9 11]

Several clinical studies implicated that eyes with LMH remain stable over time irrespective of the characteristics of epiretinal tissue and its contractive potential.[5 6 12] However, presence of LHEP was demonstrated to be related to the occurrence of photoreceptor layer defects and poor visual acuity.[6 8 9] Therefore, there is an ongoing discussion on distinct subtypes of LMHs and the role of LHEP in lamellar macular defects.

Since the evolution and progression of LHEP is poorly understood, we conducted a retrospective OCT study analysing the progression of LHEP, and correlated with intraretinal changes and visual function in eyes with LMH presenting LHEP, exclusively.

METHODS

This is a two-centre retrospective study of 34 eyes of 30 patients with LMHs associated with LHEP that was conducted to correlate morphological retinal changes and visual function during long-term follow-up. Based on the presence of LHEP on SD-OCT images at baseline visit, this subgroup of eyes was selected from a certain time point as a consecutive retrospectively reviewed series of 167 eyes of 152 patients with non-full-thickness macular holes (figure 1). Patients were seen at the Department of Ophthalmology, Ludwig-Maximilians-University Munich, Germany or at the Eye Clinic, Department of Clinical Science 'Luigi Sacco', Sacco Hospital, University of Milan, Milan, Italy between June 2008 and June 2016. The Institutional Review Boards approved the retrospective review of the patients' data. The study was conducted according to the tenets of the Declaration of Helsinki.

Patients selection

The included patients were studied retrospectively. We used the following SD-OCT criteria to diagnose a LMH: (1) irregular foveal contour, (2) defect in

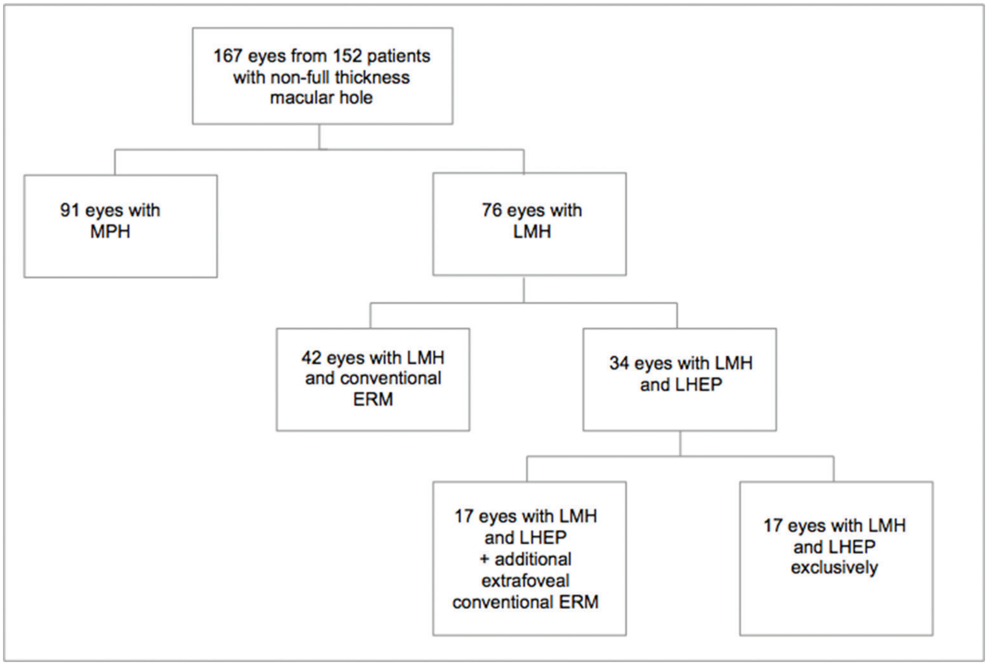

Figure 1 Flow chart of the 152 patients with non-full-thickness macular hole, among whom 34 eyes of 30 patients had a lamellar macular hole (LMH) with lamellar hole-associated epiretinal proliferation (LHEP). From these, in 17 eyes an additional extrafoveal epiretinal membrane (ERM) was seen. All eyes presented with a macular pseudohole (MPH) were excluded as well as eyes that showed a LMH without LHEP.

the inner fovea and (3) separation of inner retinal layers from outer foveal retinal layers leading to an intraretinal splitting.[13] According to Pang *et al* LHEP was defined as epiretinal material of homogeneous medium reflectivity without contractive properties on the retinal surface.[8 9] Eyes presenting with steepening of the foveal contour or verticalised foveal edges, or with an increased parafoveal retinal thickness and a normal thickness of the outer foveal retinal layers were diagnosed as macular pseudoholes and were not included in this series.[14]

Patients' charts were reviewed for age, gender, best-corrected visual acuity (BCVA), history of ocular surgery or trauma. Eyes with other macular disorders such as age-related macular degeneration, macular oedema, diabetic retinopathy or retinal vessel occlusion were excluded, or if eyes had history of intraocular surgery or ocular trauma. All patients who underwent vitrectomy during the follow-up period or were lost to follow-up for at least 6 months were excluded. Eyes that had surgery such as cataract extraction were excluded from functional analysis.

SD-OCT analysis

For SD-OCT (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) analysis, B-scans of baseline visit and each follow-up examination were retrospectively reviewed and re-evaluated for morphological characteristics as demonstrated in figure 2.

Analysing the area of LHEP, series of measurements were done by two different, masked independent retina specialists (DC and AA). SD-OCT volume scans consisted of at least 25 or 49 B-scans centred at the fovea with lateral resolution of 12 µm and axial resolution of 4 µm. Area of LHEP was measured on high magnification in each central scan of the lamellar hole at both edges of the lamellar hole using the Heidelberg Engineering Software measurement tool. According to de Jong *et al*[15] measurements were conducted for the first upper and first lower central scan in case of 25 scans, or for the second upper and second lower central scan in case of 49 scans. This procedure was performed for each SD-OCT image of each patient's visit for all included eyes. Finally, measurements of each SD-OCT image were added to get a sum of the area of LHEP at each follow-up visit.

The maximum horizontal diameter was taken at the level of the intraretinal splitting at the Henle's fibre layer and showed the widest diameter of the lamellar hole as seen on horizontal B-scans. The minimum horizontal diameter was taken at the level of the internal limiting membrane. The central retinal thickness was measured as the thinnest vertical distance between the hyper-reflective retinal pigment epithelium band and the thinnest part of the base of the lamellar hole. The integrity of the photoreceptor layer was analysed with particular regard to the ellipsoid zone. Integrity or discontinuity of the ellipsoid zone was evaluated in the same horizontal axis of SD-OCT examinations over time differentiating between 'defect present' and 'defect absent'. Furthermore, an additional extrafoveal conventional epiretinal membrane with contractive properties resulting in exerting retinal folds was documented.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics V.23.0 Software (SPSS, IBM Software Group, Chicago, Illinois, USA). Statistical significance was proven with Wilcoxon signed rank test with continuity correction, Mann-Whitney U test and Pearson's as well as Spearman's correlation. Moreover, we determined the concordance correlation coefficients (CCC) to compare the SD-OCT measurements of the two graders. Values of $p<0.05$ were considered to be statistically significant.

RESULTS

In this retrospective study, we included 34 eyes of 13 female and 21 male patients with LMHs presenting LHEP, exclusively. Patients' mean age was 76.5±9.0 years (median 77 years). The mean follow-up period was 40.5±26.2 months (median 52 months). Table 1 summarises patients' data and main functional and anatomic outcomes.

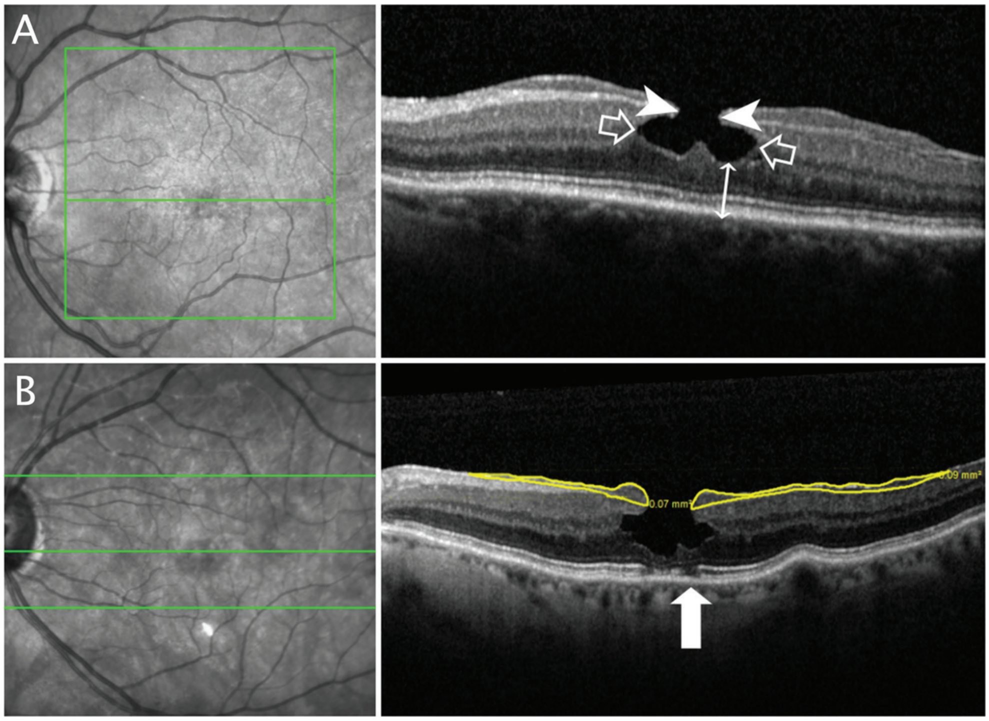

Figure 2 Spectral-domain optical coherence tomography images representing lamellar macular holes with lamellar hole-associated epiretinal proliferation (LHEP). (A) The white arrowheads show the minimum horizontal diameter, measured at the thinnest level of the internal limiting membrane. The white arrows show the maximum horizontal diameter taken at the widest level of the intraretinal splitting, the Henle's fibre layer. The double-headed arrow demonstrates the central retinal thickness. (B) The area of the LHEP (in mm^2) is measured in the central scan of the lamellar macular hole. The white arrow shows defects in the ellipsoid zone.

The appearance of the LMH with LHEP presented a pot configuration in most cases (22 of 34 eyes, 65%) according to the description of Govetto *et al*.[16] The remaining 12 eyes (35%) showed a non-pot appearance. A progression to a full-thickness macular hole during follow-up was documented in one eye after 4 years of follow-up.

Area of LHEP and horizontal hole diameter

On SD-OCT imaging, area of LHEP significantly increased during follow-up (Wilcoxon test, $p<0.001$) (figures 3A, 4). The mean area of LHEP was $0.166\pm0.171\,mm^2$ at baseline and $0.260\pm0.240\,mm^2$ at last follow-up. The CCC of analysing the area of LHEP between the two independent retina specialists was 0.97.

Minimum and maximum horizontal hole diameter showed also statistical significant progression in eyes with LMH and LHEP during follow-up period (Wilcoxon test, minimum horizontal diameter $p<0.03$; maximum horizontal diameter $p<0.004$). The mean minimum horizontal hole diameter was $463\pm124\,\mu m$ at baseline and $502\pm155\,\mu m$ at last follow-up. The mean maximum horizontal hole diameter was $818\pm301\,\mu m$ at baseline and $1010\pm366\,\mu m$ at patients' last follow-up (figure 3B). Twenty-four of 34 eyes (71%) showed morphological progression of maximum horizontal hole diameter. Only 3 of 34 eyes presented stable findings (all with a non-pot appearance), whereas 7 of 34 eyes revealed a decrease of the maximum horizontal diameter (four with a pot and three with a non-pot appearance). From these eyes, we found an increase of the area of LHEP in five of seven eyes.

The increase of LHEP area correlated significantly with the increase of maximum horizontal hole diameter (Pearson's, $r=0.417$, $p=0.015$, Spearman's rho, $r=0.355$, $p=0.040$). In details, for each micron of enlargement of the maximum horizontal hole diameter an increase of the LHEP area of $0.00026\,mm^2$ developed. Increase of maximum horizontal hole diameter correlated significantly with a worsening of BCVA (Spearman's rho, $r=0.379$, $p=0.027$; Mann-Whitney U test $p=0.027$) (figure 3C).

Retinal thickness and ellipsoid zone

Central retinal thickness was $141\pm29\,\mu m$ at baseline and $131\pm32\,\mu m$ at last follow-up. This implicated a trend towards a decrease of central retinal thickness in eyes with LMH and LHEP (Wilcoxon test, $p=0.07$).

In 22 of 34 eyes (65%), we detected defects of the photoreceptor ellipsoid zone at baseline. At the end of follow-up, defects of the ellipsoid zone were seen in 29 of 34 eyes (85%). This finding was statistically significant (Wilcoxon test, $p<0.008$). The maximum horizontal hole diameter of the lamellar defect correlated significantly with the defects of the photoreceptor layer at last follow-up (Mann-Whitney U test, $p<0.02$).

Contractive epiretinal membranes

In 17 of 34 eyes (50%), we found an additional extrafoveal conventional epiretinal membrane coexisting with LHEP and exerting tractional folds on the inner retinal layers. However, there was no significant correlation between the additional extrafoveal epiretinal membrane and the BCVA (Mann-Whitney U test, $p=0.146$). Furthermore, in eyes with extrafoveal epiretinal membranes no significant correlations were found with progression of the parameters minimum/maximum horizontal diameter of the lamellar hole and central retinal thickness (Mann-Whitney U test, minimum horizontal diameter $p=0.642$; maximum horizontal diameter $p=0.139$; central retinal thickness $p=0.436$)

as well as with the occurrence of defects in the ellipsoid zone (Mann-Whitney U test, p=0.627).

Functional outcomes

The mean BCVA at baseline was 0.30±0.16 logMAR. At patients' last visit, BCVA was 0.32±0.21 logMAR. During this period of time, there was no statistically significant visual deterioration (Wilcoxon test, p=0.53). Eyes that underwent surgery were excluded from this analysis.

The status of the lens did not change during follow-up. At baseline and at last follow-up, 27 of 34 eyes were pseudophakic, whereas 7 of 34 eyes remained phakic. There was no significant correlation between the change of BCVA and the increase of LHEP over all eyes (Spearman's rho, r=−0.136; p=0.443).

DISCUSSION

By exclusively including eyes with LMHs presenting LHEP, we were able to demonstrate that this subgroup of eyes showed a significant morphological progression during long-term follow-up. We found a significant increase of LHEP area that correlated with an enlargement of the maximum horizontal lamellar hole diameter based on SD-OCT findings during a mean follow-up period of 40.5 months. The increase of maximum horizontal hole diameter correlated with defects in the ellipsoid zone and was associated with worsening of BCVA. Eyes with a larger increase of the maximum horizontal diameter showed a worse BCVA than eyes with a smaller increase.

Our findings are consistent with other studies. Pang *et al* reported that the presence of LHEP was significantly associated with larger LMH diameter and thinner retinal thickness at the base of the LMH.[9] Recently, Govetto *et al* also demonstrated a significant increase of LHEP thickness by measuring the height of LHEP on B-scans.[16] Theodossiadis *et al* described an increase of the diameter of the LMH and a significant association between the LMH diameter increase and the presence of an epiretinal membrane.[12] However, there was no differentiation between different kinds of epiretinal proliferation like contractive epiretinal membranes and LHEP in early reports.

It was previously reported that eyes with LMH and LHEP show significantly poorer mean BCVA in comparison to eyes without LHEP.[6 9] This might be explained by the presence of defects in the ellipsoid zone, which are demonstrated to appear more often in eyes with LHEP compared with eyes without LHEP.[6 9 16] In our study, defects in the ellipsoid zone were seen significantly more often at last follow-up and were correlated with maximum horizontal diameter. During follow-up, BCVA remained stable. Since operated eyes were excluded from this analysis, the lack of association between increase of LHEP area and BCVA might be a bias based on the selection of the patients for surgery.

The evolution of LMH was suggested to be a slow, chronic, degenerative process causing loss of retinal tissue and disruption of the ellipsoid layer.[16] It might be that whenever the degenerative process deepens into the retina causing an enlargement of the cavitated area, LHEP increases like a reactive healing process. Therefore, measurement of maximum horizontal hole diameter is a reliable parameter of evolution and progression of a LMH with LHEP because it involves deeper retinal layers than measurement of minimum horizontal hole diameter, specifically the cavitated area and not the edges of the hole. However, the pathogenesis of LMH still remains controversial. By immunocytochemical and ultrastructural findings, it was hypothesised that LHEP might be related to vitreous derived cells like hyalocytes and fibroblasts.[7 10] However, the formation of an LMH might also be initiated as a healing process and subsequently involve retinal glial cells like Müller cells.[9 11]

Our findings emphasise that in half of all cases an additional contractive epiretinal membrane is associated with LHEP (50%). The prevalence of an additional epiretinal membrane differs among studies.[6 7 14 17] Whereas Govetto *et al* reported signs of traction in only 15% of eyes with LMH and LHEP.[16] dell'Omo *et al* found contractive epiretinal membranes without LHEP in 51%, epiretinal membranes associated with LHEP in 36% and LHEP alone in 13% of all examined eyes.[17] Density, orientation and number of recorded B-scans are in fact crucial factors for confirming or excluding the presence of each type of epiretinal material. To our best knowledge, different studies on LMHs use different criteria for the definition of LMHs and macular pseudoholes. Differences reported on the presence of epiretinal material in LMHs are partly due to a pending consensus of the current concept of LMHs.

Furthermore, indication for surgical treatment of LMH is an ongoing debate. It was recently reported that the presence of LHEP influences morphological and functional features of these eyes in comparison to other subgroups of LMHs. In detail, presence of LHEP was demonstrated to be related with occurrence of photoreceptor layer defects and poor visual acuity.[6 8 9] Zampedri *et al* presented morphological changes and involvement of the outer retinal layers during a 2-year follow-up.[18] It was hypothesised that LMH with LHEP might be a more severe clinical entity compared with LMH with contractive epiretinal membranes. Our findings are consistent with these reports by demonstrating a significant increase of LHEP area that correlated with an enlargement of

Table 1 Patient data and main functional and anatomic outcomes

Characteristic	n	p-Value
No. of eyes	34	
Gender		
Male (%)	21 (62)	
Female (%)	13 (38)	
Age, years	76.5±9.0 (57–91)	
Mean follow-up, months	40.5±26.2 (6–87)	
BCVA, logMAR		0.53
Baseline	0.30±0.16	
Last follow-up	0.32±0.21	
Lens status		
Phakia (%)	7 (21)	
Pseudophakia (%)	27 (79)	
Area of LHEP, mm^2		<0.01*
Baseline	0.166±0.171	
Last follow-up	0.260±0.240	
Minimum horizontal hole diameter, µm		<0.03*
Baseline	463±124	
Last follow-up	502±155	
Maximum horizontal hole diameter, µm		<0.01*
Baseline	818±301	
Last follow-up	1010±366	
Central retinal thickness, µm		0.07
Baseline	141±29	
Last follow-up	131±32	
Defects in ellipsoid zone (%)		<0.01*
Baseline	22 (65)	
Last follow-up	29 (85)	

*Statistically significant.

BCVA, best-corrected visual acuity; LHEP, lamellar hole-associated epiretinal proliferation; LMH, lamellar macular hole.

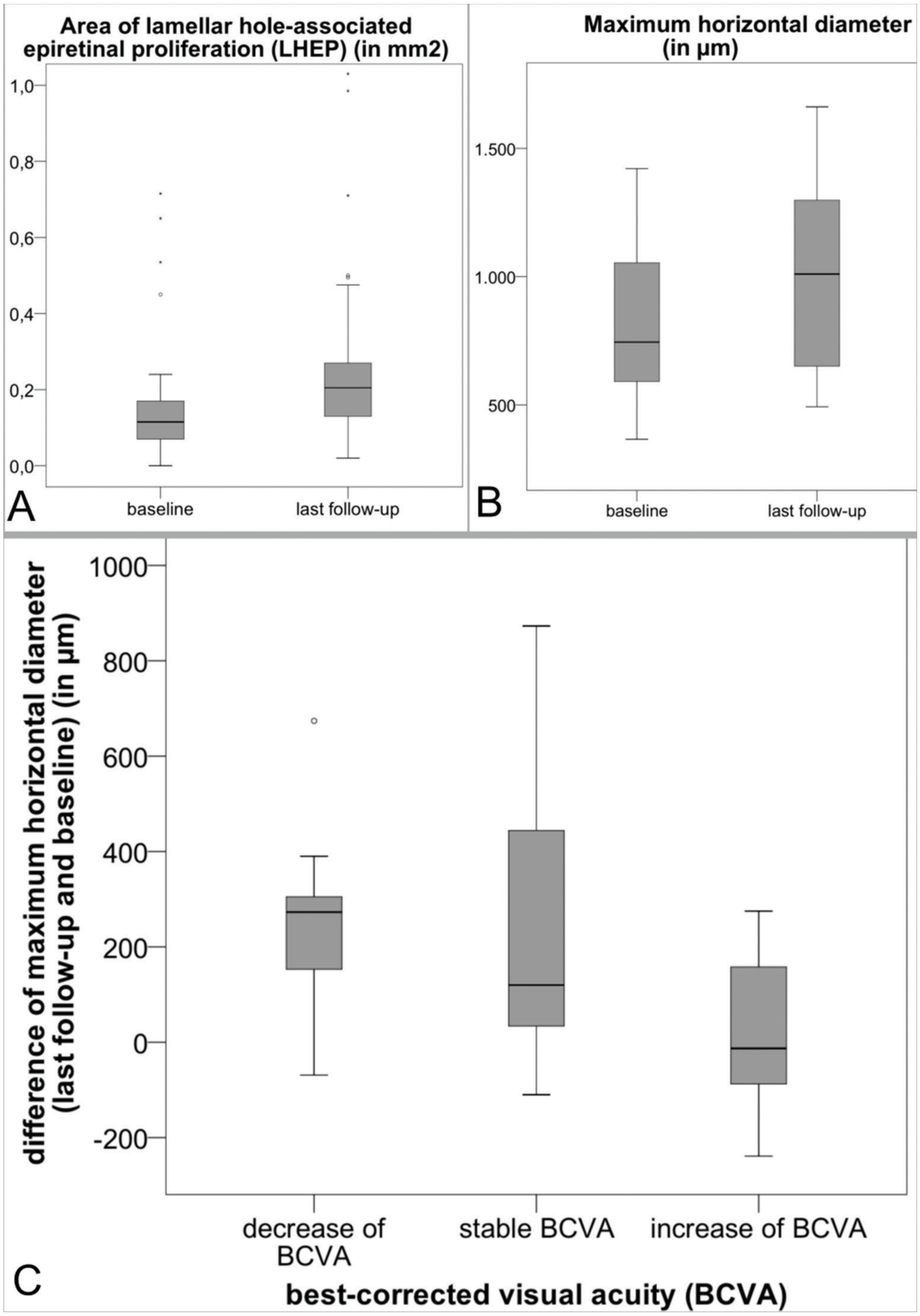

Figure 3 (A) The two box plots present the area of lamellar hole-associated epiretinal proliferation (LHEP) in eyes with lamellar macular hole at baseline and at last follow-up. The increase of the LHEP area between baseline and last follow-up was statistically significant (Wilcoxon test, p<0.001). (B) The two box plots demonstrate the maximum horizontal diameter, measured at the level of the intraretinal splitting, at baseline and last follow-up. There was a significant increase of the maximum horizontal diameter during follow-up (Wilcoxon test, p<0.004). (C) The box plots illustrate the correlation between best-corrected visual acuity (BCVA) and maximum horizontal diameter at baseline and at last follow-up. Patients were divided into three groups: those, who showed a decrease of BCVA during follow-up, the ones, who had a stable BCVA and the other, who had an increase of BCVA during time. Values of the maximum horizontal diameter, calculated from the difference between maximum horizontal diameter at the last follow-up and maximum horizontal diameter at baseline, are shown on the y-axis. There was a significant correlation of decrease of BCVA with increase of maximum horizontal diameter and increase of BCVA with decrease of maximum horizontal diameter (Mann-Whitney U test, p=0.027).

the maximum horizontal hole diameter and presence of ellipsoid zone defects.

However, dell'Omo *et al* postulated that characteristics of epiretinal material in LMHs does not influence the natural course of the disease or the response to surgery.[17] This is in accordance with the previous studies that emphasised LMHs as stable condition.[2 5 6 14] Given that there still are different classifications used to diagnose subgroups of LMHs and macular pseudoholes, recommendation for surgical intervention remains controversial. Whereas some studies report on

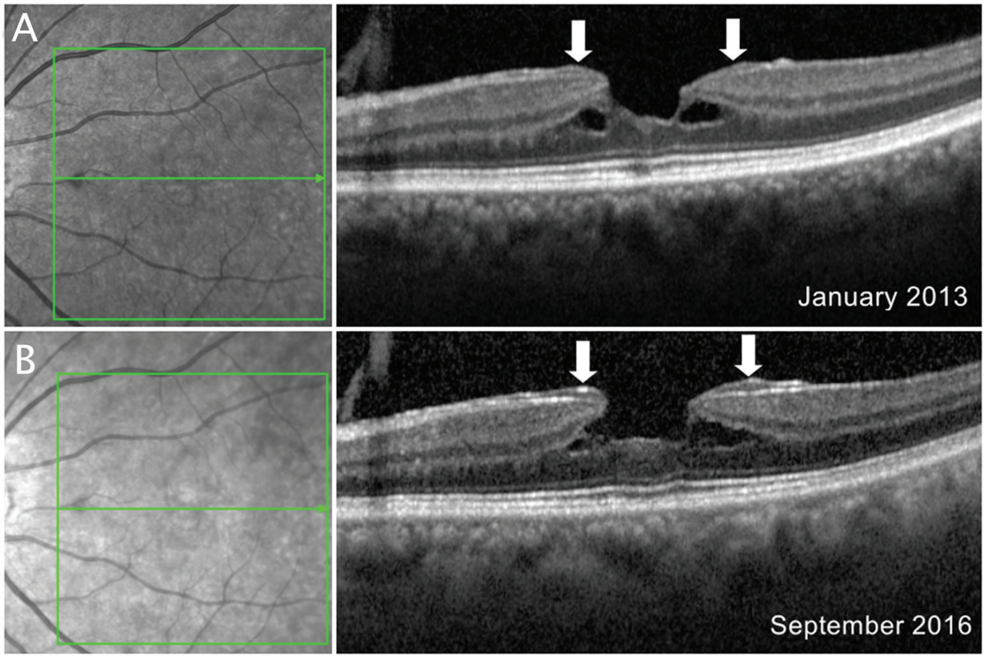

Figure 4 (A) Spectral-domain optical coherence tomography (SD-OCT) images of a female aged 63 years presenting a lamellar macular hole with lamellar hole-associated epiretinal proliferation (LHEP). (B) During a follow-up period of 3 years, there was an increase of the LHEP area (white arrows). The maximum horizontal diameter increased as well.

functional and morphological improvement by performing vitrectomy with peeling of both the epiretinal membrane and the internal limiting membrane,[19–25] others concluded that surgical intervention is not recommended.[2 5 6 14]

The strengths of this study are the homogenous series of eyes diagnosed by using the classification of Duker *et al* and Gaudric *et al* presenting LMH with LHEP exclusively, and the long-term follow-up of 40.5 months (mean; median 52 months).[13 14] The limitations of our study were mostly related to the inclusion criteria and the strict classification of LMHs that resulted in a limited number of eyes. Furthermore, area of LHEP, maximum and minimum horizontal diameter and central foveal thickness were manually measured. However, the CCC of analysing the area of LHEP between the two independent, blinded examiners was high.

In summary, our findings emphasise that LMH with LHEP show morphological progression during long-term follow-up. We demonstrated that the area of LHEP increased over time and correlated with an enlargement of the maximum horizontal hole diameter and defects in the ellipsoid zone both associated with a deterioration of visual function. We conclude that a new classification of subgroups of eyes with LMHs might me helpful to establish prognostic factors and to identify patients who are more suitable for macular surgery than others.

Contributors Substantial contributions to the conception or design of the work: DC, RGS, MGC and FB. Acquisition of data: DC, AA and VL. Analysis and interpretation of data: DC, RGS, MGC and FB. Drafting the work or revising it critically for important intellectual content: DC, RGS, SP, GS and FB. Final approval of the version published: all authors.

Competing interests None declared.

Patient consent Retrospective nature of the study.

Ethics approval Ethics committee of the medical faculty of the Ludwigs-Maximilians-University Munich.

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