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RETINAL DISORDERS

Lamellar macular holes in the eyes with pathological myopia

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Abstract

Purpose To study the natural history and morphologic characteristics of lamellar macular holes (LMHs) in the eyes with pathological myopia.

Methods Retrospective observational case series of 44 eyes of 44 patients examined at a single institutional vitreoretinal practice. The included eyes must present an irregular foveal contour and schitic or cavitated lamellar separation of neurosensory retina on spectral-domain optical coherence tomography (SD-OCT) and an area of increased autofluorescence on blue fundus autofluorescence (B-FAF) to be included. Presence of retinoschisis and posterior staphyloma, posterior vitreous status, changes of logarithm of minimum angle of resolution best-corrected visual acuity (BCVA), and changes of morphologic characteristics were evaluated.

Results The mean follow-up period was 50.1 ± 28.9 months; 75% of the enrolled patients were female. At baseline, a standard epiretinal membrane (ERM) was detected in 93.2%, lamellar hole-associated epiretinal proliferation (LHEP) in 75%, and concomitant ERM and LHEP in 68.2% of the eyes, respectively. Visual acuity did not correlate with LMH diameters but correlated with central foveal thickness ($p < 0.001$). During the follow-up, the morphologic and functional parameters studied were relatively stable/improved in 60% of the eyes independently from the associated epiretinal material. Four eyes evolved to full-thickness (FT) MHs whereas spontaneous improvement was observed in five cases.

Conclusions LMHs in highly myopic eyes are more prevalent in females, are frequently associated with ERM and LHEP, and show substantial stability of BCVA and the anatomic parameters evaluated with B-FAF and SD-OCT over years-long follow-up.

Keywords Pathological myopia · Lamellar macular holes · Blue fundus autofluorescence · Optical coherence tomography · Epiretinal membrane · Lamellar hole-associated epiretinal proliferation

Introduction

Myopia is a common ocular abnormality that affects 20–40% of adults worldwide [1, 2]. The condition in which myopic elongation of the globe is ≥ 26.5 mm and degenerative changes in the sclera, choroid, retinal pigment epithelium (RPE), and retina develop is defined pathological myopia (PM) [3–5].

Long-term studies suggest that approximately 40% of highly myopic eyes develop signs of PM at the macula including lacquer cracks, choroidal neovascularization (CNV), retinoschisis, vitreomacular traction, and lamellar (LMHs) or full-thickness macular holes (FTMHs) [6–9].

Imaging modalities like optical coherence tomography (OCT) [8, 9] and blue fundus autofluorescence (B-FAF) [10] have been widely used to study the morphologic abnormalities of the macular region in the eyes with PM, since a clear view

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of the posterior pole with biomicroscopy in these eyes may be hindered by the absence of a uniform RPE background. However, studies specifically focused on LMHs in the eyes with PM are limited [11–13] and we are unaware of previous reports regarding the natural history of LMHs in the eyes with PM evaluated with B-FAF and OCT.

In emmetropic eyes, when imaged with OCT, LMHs are usually associated with epiretinal materials that can be thin and highly reflective (the so-called standard epiretinal membrane [ERM]) or of medium reflectivity with focal variations in thickness (the so-called lamellar hole-associated epiretinal proliferation [LHEP]) [14–20]. When imaged with B-FAF, LMHs are characterized by an increased autofluorescent signal [14, 17].

Peculiar characteristics of the eyes with PM, like posterior staphyloma, vitreous cortex schisis, and macular schisis may theoretically have an influence and cause some differences on the morphology and natural evolution of LMHs observed in these eyes in comparison to emmetropic eyes. Furthermore, at present, few data regarding the type of epiretinal tissue (either ERM or LHEP) associated with LMHs in PM are available in the literature [12, 13]. Therefore, studying these features and comparing B-FAF and OCT findings in the eyes with PM with those obtained in nonmyopic eyes would be interesting.

The purpose of this study was to retrospectively investigate the natural history of LMHs in the eyes with PM using both spectral-domain (SD)-OCT and B-FAF imaging.

Methods

We conducted a retrospective case series of patients affected by PM and LMHs seen at the University of Molise, Campobasso, from January 1, 2009, to October 31, 2016. All subjects were treated in accordance with the Declaration of Helsinki. This study was approved by the Institutional Review Board of the University of Molise. Because of the retrospective nature of the study, formal consent from participants was not required.

The inclusion criteria were (1) myopic refractive error (spherical equivalent) > -8.0 D or axial length ≥ 26.5 mm; (2) presence of a LMH as assessed by OCT and B-FAF; and (3) minimum follow-up period of 1 year.

The SD-OCT criteria used to diagnose LMHs were as follows: (1) an irregular foveal contour or defect in the inner fovea; (2) lamellar separation of the neurosensory retina ("cavitated" or "schitic" in appearance) in at least one scan; and (3) the absence of a FT foveal defect.

The B-FAF criterion used to diagnose LMHs was an area of increased autofluorescent signal that co-localized with the inner defect observed in the fovea and that was not attributable to an intraretinal cyst based on OCT images.

On the basis of OCT imaging, the epiretinal material associated with the LMH was defined as standard ERM or LHEP [19]. Other OCT morphologic characteristics analyzed included the relation of the vitreous cortex with the surface of the macula (attached/detached), the presence of retinal wrinkling, the presence of disruption of the external limiting membrane (ELM), ellipsoid and interdigitation zones (EZ and IZ), and central foveal thickness (CFT).

The exclusion criteria were history of retinal detachment, age-related macular degeneration, diabetic retinopathy, retinal vein occlusion, uveitis, trauma, previous pars plana vitrectomy, and a refractive error of ≤ -8 diopters of spherical equivalent; CNV involving the macula; lacquer cracks encroaching the fovea; chorioretinal/RPE atrophy at the fovea; and gross vitreous opacities hindering a clear view of the posterior pole.

Patient characteristics, including age, sex, lens status, and refractive error, were recorded at baseline. Axial length measurements were obtained by using partial optical coherence inferometry (IOLMaster; Carl Zeiss Meditec, Inc.). The presence and type of posterior staphyloma were determined by ophthalmoscopy [21] and SD-OCT [22, 23] and classified according to the criteria proposed by Curtin [21].

The logarithm of the minimum angle of resolution (logMAR) best-corrected visual acuity (BCVA) was tested at each visit using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 4 m, along with evaluation of cataract progression in phakic eyes.

All B-FAF and OCT images were collected using the Heidelberg Spectralis system (Heidelberg Engineering, Heidelberg, Germany). The "follow-up" function was used from the baseline to the time of the most recent encounter.

The OCT recording protocol covered an area of 30 or 20° horizontally × 20° vertically (97 horizontal sections approximately 60 μm apart). Blue fundus autofluorescence (excitation wavelength at 488 nm and barrier filter at 500 nm) images (35°) were obtained at each follow-up examination.

The horizontal and vertical LMH diameters were measured on B-FAF images (areas of increased autofluorescence) and on OCT images as the distance between the central borders of the outer plexiform layer, as described in a previous study (Fig. 1) [17]; B-FAF was also used to test the presence of retinal vessel printings (RVPs) [17].

Central foveal thickness was automatically measured by the software, whereas diameter measurements were obtained manually with the built-in manual caliper function on high magnification after adjusting the scale to 1:1 μm.

Anatomic progression was defined as a widening of the LMH by more than 50 μm, a deepening of the LMH by more than 20 μm, and/or the development of a FT macular hole. Anatomic regression was defined as a reduction of the lesion's size by more than 50 μm or thickening of the CFT by more than 20 μm.

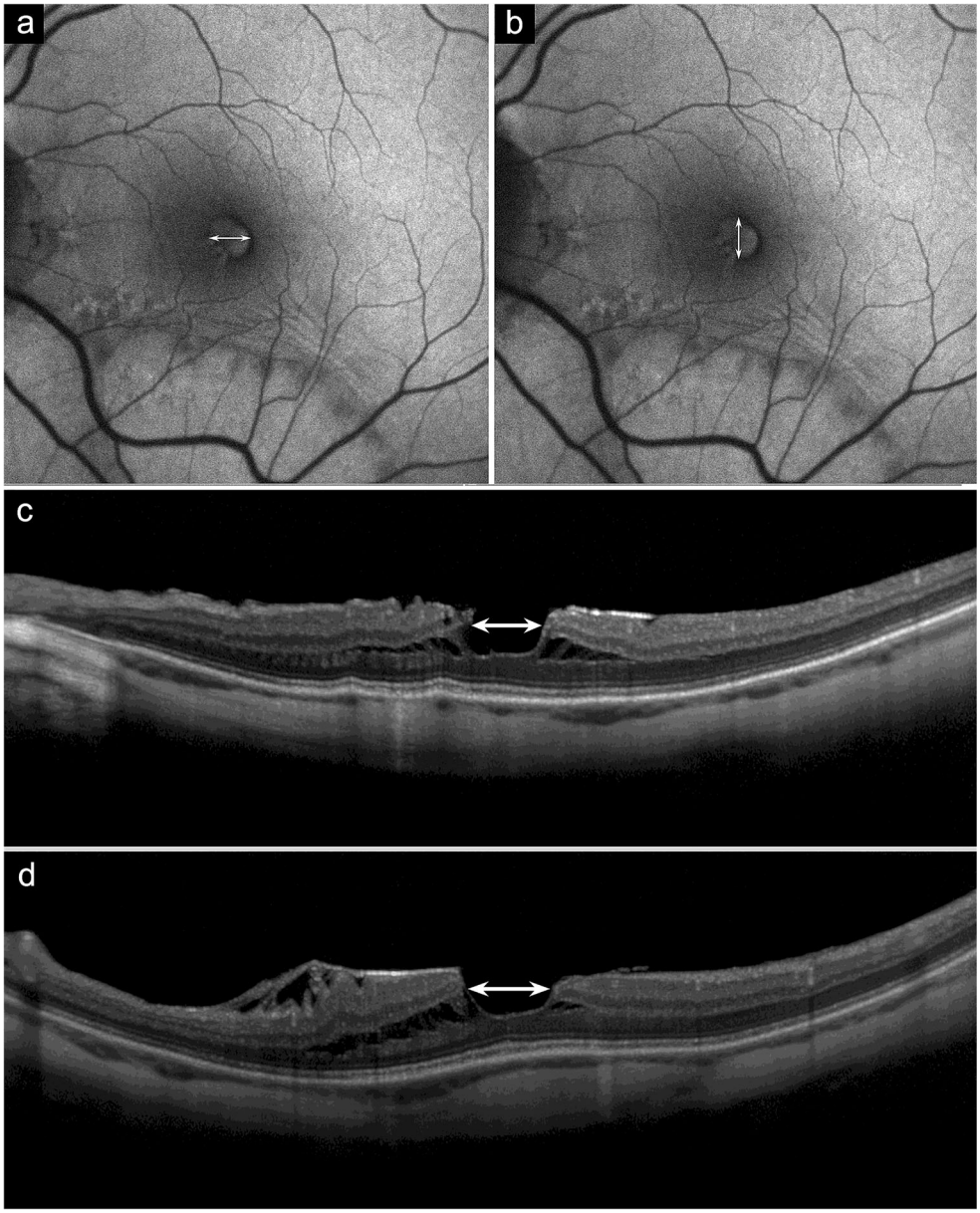

Fig. 1 Blue fundus autofluorescence (B-FAF)-based and optical coherence tomography (OCT)-based measurements of diameters of lamellar macular holes (LMHs) in an eye with high myopia. **a**, **b** Horizontal and vertical diameters of the hyperautofluorescent area related to the hole on B-FAF images. **c**, **d** On OCT images, the diameters are measured as the distance between the central borders of the outer plexiform layer

Statistical analysis

We compared the characteristics of the eyes with and without LHEP using Student's *t* test for continuous variables and a chi-square test for dichotomous variables. The correlation between BCVA and morphometric continuous variables was estimated using standardized coefficients in structural equation models that account for repeated measures within individuals. Linear mixed models, with individuals as a random effect, were used to estimate the follow-up changes in functional and anatomic variables, as well as the effects of covariates of interest. All analyses were conducted using the Stata 14.1 software (StataCorp 2015, College Station, TX, USA).

Results

A total of 44 eyes from 44 patients met the inclusion criteria and our definition of LMH and were enrolled in the study. The mean age of the patients at entry was 62.3 ± 10.4 years of age (range, 33 to 83 years). Of the 44 included patients, 11 (25%) were male and 33 (75%) were female.

At baseline, 19 (43.2%) eyes were phakic and 25 (56.8%) eyes were pseudophakic; during the follow-up, 7 phakic eyes underwent cataract extraction and IOL implantation without complications**.** The mean refractive error (considering preoperative values for pseudophakic eyes) was − 14.91 ± 3.76 D (range, − 8.50 to − 22 D) and the mean axial length was 30.05 ± 2.21 mm (range, 26.81 to 34.32 mm).

Table 1 Blue fundus autofluorescence/optical coherence tomography findings and type of epiretinal materials associated with lamellar macular holes at baseline

	Total ($n = 44$) Mean (SD)	LHEP ($n = 33$) Mean (SD)	No LHEP ($n = 11$) Mean (SD)	p value
Axial length	30.05 (2.21)	30.01 (2.32)	30.23 (1.95)	0.748[a]
Refraction	− 14.91 (3.76)	− 14.67 (4.09)	− 15.64 (2.54)	0.446[a]
B-FAF area (mm^2)	0.18 (0.16)	0.20 (0.18)	0.12 (0.11)	0.20[a]
B-FAF horizontal diameter (μm)	392.93 (209.75)	408.85 (218.78)	339.75 (171.40)	0.31[a]
B-FAF vertical diameter (μm)	386.59 (198.85)	404.27 (211.81)	333.54 (149.46)	0.31[a]
OCT horizontal diameter (μm)	312.38 (173.29)	332.87 (187.03)	250.90 (107.90)	0.17[a]
OCT vertical diameter (μm)	310.61 (180.61)	326.27 (189.44)	263.63 (149.0)	0.32[a]
OCT central foveal thickness (μm)	180.20 (52.90)	169.24 (48.42)	213.09 (54.24)	0.06[a]
Posterior cortex visible on OCT	8 (18.2%)	6 (18.2%)	2 (18.2%)	0.906[b]
Standard ERM	41 (93.2%)	30 (90.9%)	11 (100%)	0.280[b]
Sharp-edged split	29 (65.9%)	21 (63.6%)	8 (72.7%)	0.131[b]
Round-edged cavitation	21 (47.7%)	17 (51.5%)	4 (36.4%)	0.365[b]
Retinoschisis	9 (20.5%)	7 (21.2%)	2 (18.1%)	0.726[b]
ORB disruption on OCT	11 (25%)	11 (33.3%)	0 (0)	0.022[b]*
Retinal wrinkling	19 (43.2%)	11 (33.3%)	8 (72.7%)	0.043[b]*
Retinal vessel printings	0 (0)	0 (0)	0 (0)	n.a.
Staphyloma	37(84.1%)	28 (84.8%)	9 (81.8%)	0.325[b]

B-FAF blue fundus autofluorescence, *ERM* epiretinal membrane, *LHEP* lamellar hole-associated epiretinal proliferation, *OCT* optical coherence tomography, *ORB* outer retinal bands

*Statistically significant

[a] *t* test

[b] X^2 test

The mean follow-up period was 50.1 ± 28.9 months with a range of 12 to 96 months. At baseline and at 48-month follow-up, the mean logMAR BCVA of the whole sample was 0.30 ± 0.25 and 0.33 ± 0.38, respectively, and did not differ significantly between the group with and without LHEP (0.32 ± 0.27 and 0.28 ± 0.18, $p = 0.571$ and 0.35 ± 0.28 and 0.28 ± 0.21, $p = 0.232$, respectively, Fig. 3). Visual acuity remained unchanged after operation in four and improved in three of the eyes that underwent cataract surgery.

At baseline, a standard ERM was detected in 41 (93.2%) eyes and LHEP in 33 (75%) eyes. Thirty eyes (68.2%) presented with both ERM and LHEP. Standard ERM alone was found in 11 (25%) eyes, whereas LHEP alone was found in 3 (6.8%) eyes. All eyes in this series presented either LHEP or ERM. Eight (72.7%) and 4 (36.4%) out of the 11 cases with ERM alone and 21 (63.6%) and 17 (51.5%) out of 33 cases with LHEP showed sharp-edged split and round-edged cavitation of the margins of the LMH, respectively. Overall sharp-edged split was found in 23, round-edged cavitation in 15, and concomitant split and cavitation in 6 cases.

The group with LHEP ($n = 33$) and the group without LHEP ($n = 11$) did not differ for any of the following parameters: axial length, refraction, B-FAF horizontal and vertical diameters, and OCT horizontal and vertical diameters. Disruption of the outer retinal bands (ORBs), i.e., ELM, EZ, and IZ, was significantly more common in the eyes with LHEP ($p = .022$), whereas retinal wrinkling was more common in the eyes without LHEP ($p = .043$). The central fovea was thinner in the eyes with LHEP, but this was borderline for statistical significance ($p = .06$). Table 1 summarizes the OCT and B-FAF findings of the sample at baseline.

Eight eyes (18.2%) showed macular retinoschisis and 36 out of 44 eyes (81.8%) had a posterior staphyloma. The type II staphyloma was the most prevalent (16 eyes, 44.4%), followed by type I (8 cases, 22.2%) and type IX (5 cases, 13.9%). Types III, IV, and VII were observed in three, two, and two cases, respectively (Fig. 2).

During the follow-up, the parameters were relatively stable in 60% of the eyes. Figure 3 shows the changes that occurred over time in the groups with and without LHEP. The data were calculated up to 48 months, when at least ten patients were followed up overall, making the mean values estimable.

Spontaneous improvement was observed in 5 eyes, stability in 21 eyes (Fig. 4), and enlargement/deepening of the LMHs in 18 eyes. Among the five eyes that improved, three showed both standard ERM and LHEP and both sharp-edged split and round-edged cavitation. Among the eyes that worsened, four, i.e., 9% of the whole sample, evolved to FTMH (Fig. 5). All these four eyes presented with both ERM and LHEP and posterior staphyloma and all but one presented with retinoschisis. The mean time (± SD) of evolution to

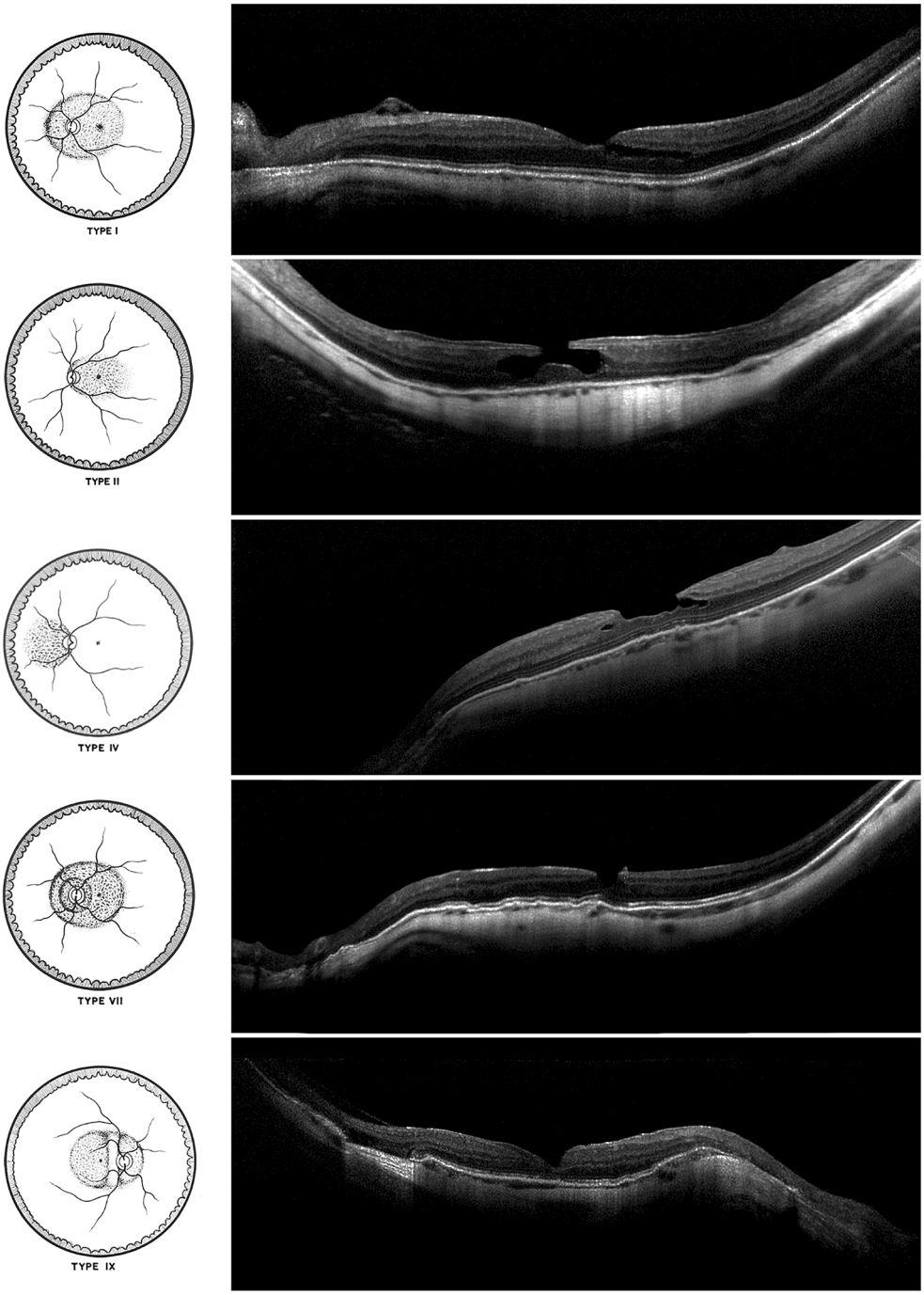

Fig. 2 Types of posterior staphyloma as classified by Curtin and corresponding optical coherence tomography images in eyes with pathological myopia and lamellar macular holes [21]

FTMH after baseline observation was 36 ± 8.48 months. Only one eye showed spontaneous resolution of the LMH by the last visit.

Correlations between functional and anatomic variables

There was a good correlation between B-FAF and SD-OCT regarding both the horizontal and vertical diameters of the holes ($r = 0.69$ and 0.78, respectively, $p < 0.001$). The logMAR BCVA did not correlate with LMH diameters (Pearson r between 0.00 and 0.09) but correlated moderately with CFT ($r = -0.35$, $p < 0.001$).

In univariate regression analyses with the baseline logMAR BCVA as the response variable, there was no significant association between BCVA and LHEP, retinoschisis, and an adherent posterior cortex ($p > 0.1$ for all analyses). On the contrary, disruption of each of the ORBs was associated with reduced BCVA (ELM 0.19 logMAR, $p = 0.009$; EZ 0.17 logMAR, $p = 0.029$; IZ 0.15 logMAR, $p = 0.028$).

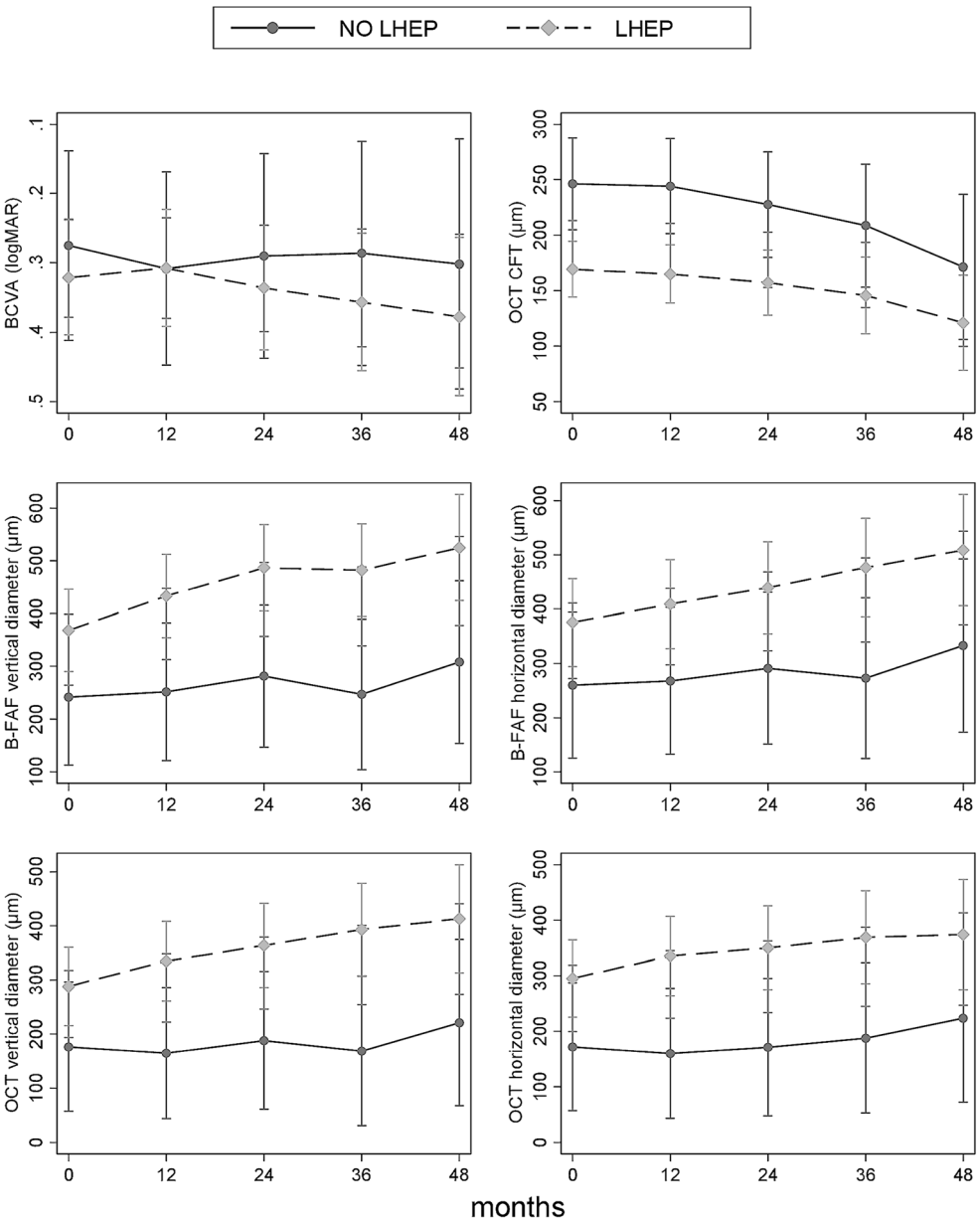

Fig. 3 Baseline and follow-up values (vertical bar: standard error) of logarithm of the minimum angle of resolution (logMAR) best-corrected visual acuity (BCVA), central foveal thickness (CFT), and hole diameters measured with blue fundus autofluorescence (B-FAF) and optical coherence tomography (OCT) in eyes with ($n = 33$, dashed line) and without lamellar hole epiretinal proliferation (LHEP, $n = 11$, solid line). Ninety-three percent of the whole sample showed an associated standard epiretinal membrane. Estimates are derived from a linear mixed model

No predictor of progression of BCVA or OCT thickness could be identified.

Discussion

Pathologic myopia is a major cause of legal blindness worldwide, with a prevalence of 0.2 to 0.4% in the general population of the USA and Europe and 1% of the general population in Japan, with women affected more frequently than men [1, 2]. Regarding the presence of LMHs in the context of PM, females represented, respectively, 85.7 and 60% of the samples in two previous series [11, 12] and 78% in the current series. The female predilection for LMH, as a manifestation of PM, is presumably in keeping with the observation that the odds of PM are significantly greater among women than among males [4]. However, it has to be noted that a higher percentage of LMH in females than in males, ranging from 51.1 to 65.1%, is reported for nonmyopic eyes as well [15–18].

Recently, after the works of Pang et al. [19] and Govetto et al. [16], study groups favor to recognize two main subtypes of LMHs in emmetropic eyes, that is "tractional" and "degenerative" LMHs. The former subtype usually features a standard ERM, sharp-edged split of margins of the hole, and intact ORBs, while the latter features the presence of LHEP, round-edged cavitation, foveal bump, and disrupted ORBs. Nevertheless, overlapping forms of these two subtypes

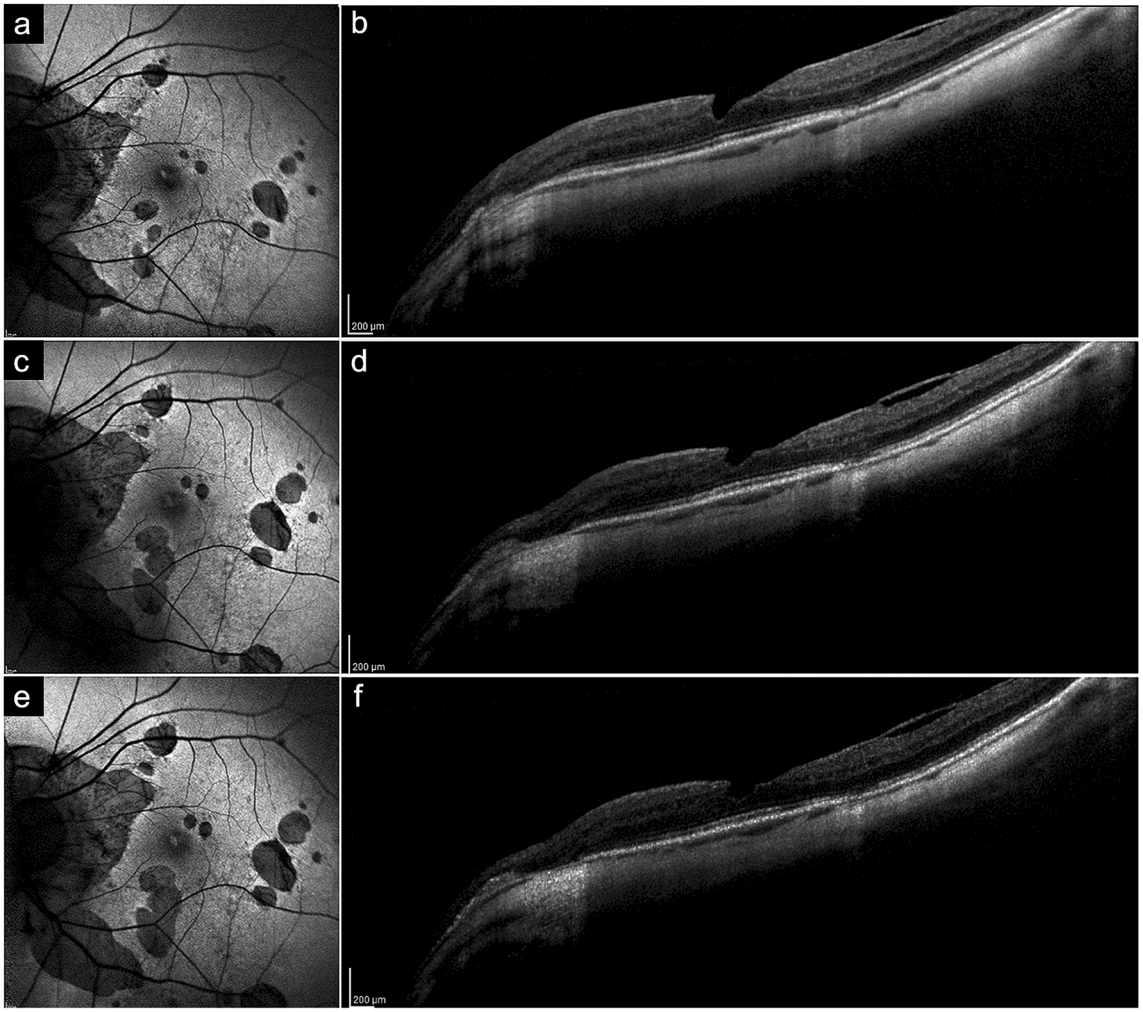

Fig. 4 Serial blue fundus autofluorescence (B-FAF) and eye-tracked optical coherence tomography (OCT) images of a 57-year-old man affected by pathological myopia complicated by lamellar macular hole showing stability of the B-FAF and OCT features over the duration of 72 months of retrospective follow-up. **a** B-FAF and **b** OCT images at baseline. **c** At 48 months of follow-up, an enlargement of the areas of retinal pigment epithelium atrophy was observed on the B-FAF image but the morphology of the hole, both on B-FAF and OCT images (**d**), was unchanged. (**e, f**) Two years later, the appearance of the hole looked similar on both B-FAF and OCT images. BCVA remained stable at 0.1 logMAR throughout the follow-up

are possible. For example, the concomitant presence of a standard ERM and LHEP [16, 17, 20], intact ORBs in presence of LHEP, and blue fundus autofluorescence findings similar in the two subtypes have been reported [17] in emmetropic eyes. The findings we report in the current study seem to highlight that a clear distinction between "tractional" and "degenerative" LMH is even more difficult to be made in the eyes with PM.

Similar to what was observed in nonmyopic eyes and in agreement with Frisina et al. [12], we found that an epiretinal material was always associated with LMHs. However, in contrast to their report (LHEP, in 42.5% of cases), we found that 75% of the cases showed LHEP. This percentage is similar to that reported recently by Lai et al. [13] and substantially higher than that reported for nonmyopic eyes, ranging from 30.5 to 48.8% [15–18]. It has been proposed that stronger tractional forces on the retina due to elongation of the globe and an attached posterior hyaloid may represent favorable conditions to promote LHEP development in highly myopic eyes [13]. Indeed, we found the coexistence of ERM and LHEP in more than two-thirds of cases of this series, while it is reported to range from 10.78 to 46% in nonmyopic eyes with LMH [15–20]. Of note, 65.6% of the cases with LHEP, an epiretinal tissue with alleged scarce contractile properties, showed sharp-edged split of the margins of the LMH. On the other hand, a standard ERM was present in all except three of the cases showing a round-edged cavitation of the hole, a feature usually associated with "degenerative" LMH in nonmyopic eyes.

The eyes with and without LHEP did not differ for any parameter except for disruption of the ORBs, which was more common in the eyes with LHEP, and retinal wrinkling, which

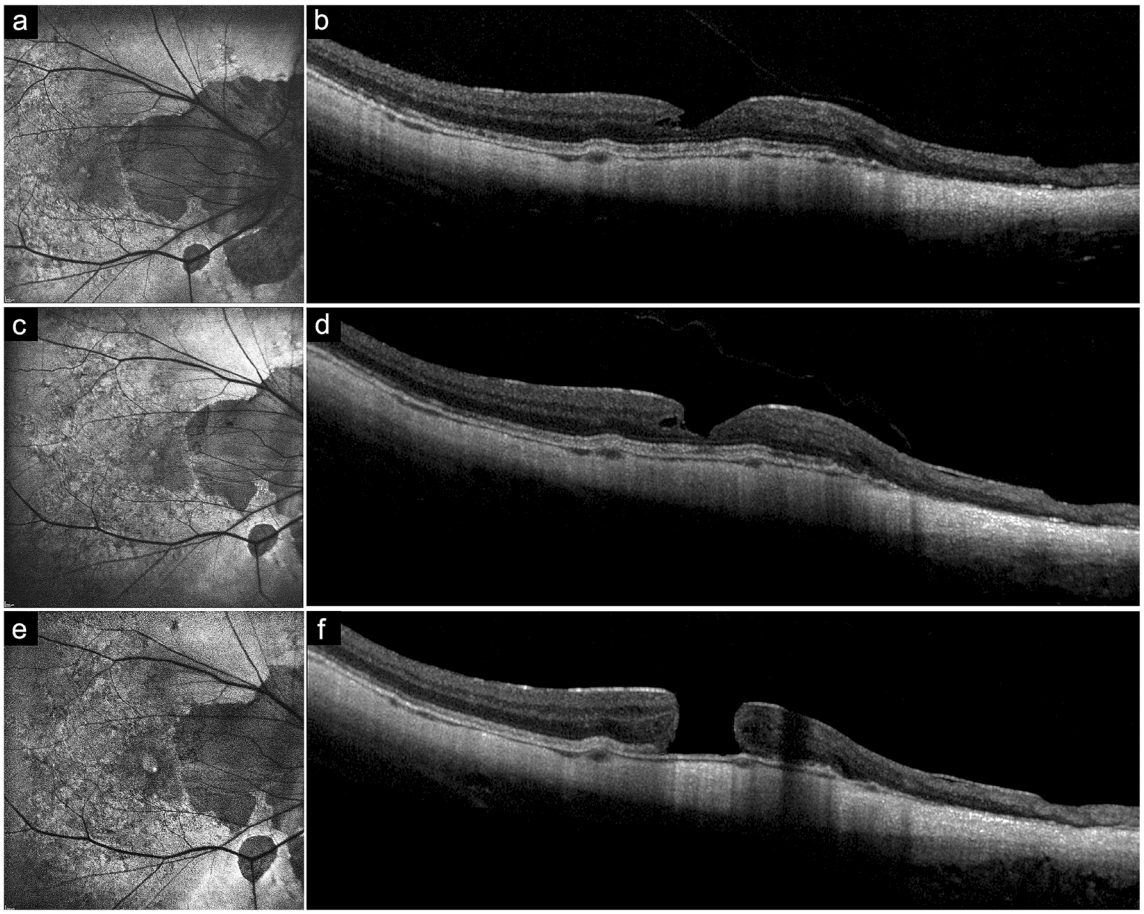

Fig. 5 Serial blue fundus autofluorescence (B-FAF) and eye-tracked optical coherence tomography (OCT) images showing the evolution of a LMH to a full-thickness macular hole (FTMH) in an eye with pathological myopia. **a** At baseline, an area of increased B-FAF was observed in correspondence of the lamellar hole shown on OCT (**b**). BCVA was 0.8 logMAR. One year later, the appearance of the hole on B-FAF was similar (**c**), but thinning of the central retinal thickness was visible on OCT (**d**). BCVA remained at 0.8 logMAR. Four years after the first examination, B-FAF imaging revealed an enlargement of the area of increased autofluorescence corresponding to the hole (**e**). On OCT imaging (**f**), a FTMH is observed. BCVA was reduced to 1 logMAR

was observed more frequently in the eyes with ERM alone. Of note, the horizontal and vertical LMH diameters measured on SD-OCT or on B-FAF images did not differ significantly between the group with and without LHEP, a result similar to that previously reported for nonmyopic eyes [17].

The CFT was substantially thinner in the eyes with LHEP than in those without, but that difference did not reach statistical significance. Conversely, a thinner CFT has been invariably reported in nonmyopic eyes with LMH and LHEP, compared to the eyes with LMH and standard ERM [14–20]. It is possible that in highly myopic eyes, the thinning of the central retina, secondary to centrifugal tractional forces related to the LMH, is in part counteracted by the antero-posterior stretching of the central retina. This stretching is caused by inward traction on one side (exerted by epiretinal membranes and vitreal adhesions/tractions) and by outward traction on the other side (exerted by the progressive elongation of the globe/posterior staphyloma) and it might well mask a progressive central retinal thinning.

Considering the whole sample, only 9% of the eyes progressed to FTMH. Nevertheless, this percentage is substantially higher than that reported for nonmyopic eyes, among which the evolution from LMH to FTMH is an extremely rare event, occurring in 1% to less than 4% of cases [14–19]. This higher percentage of LMH evolving to FTMH might be related to the concomitant presence of tangential and antero-posterior tractional forces (epiretinal membranes and staphyloma, respectively) acting on the fovea of the eyes with PM. In fact, in keeping with the data reported in the literature [22], 84% of the eyes of this series presented with posterior staphyloma. The four eyes that progressed to FTMH all had staphyloma and three out of four also had retinoschisis, an alleged predisposing factor to formation of both LMH and FTMH [24].

As far as the B-FAF findings are concerned, we found, as observed for nonmyopic eyes [17], a strong correlation between the horizontal and vertical diameters of the holes measured on B-FAF and SD-OCT scans (as the distance between

the central borders of the OPL). Therefore, our hypothesis that the increased autofluorescent signal observed in the presence of a LMH may be, at least in part, related to the "missing" OPL (the layer containing Henle's fibers, where macular pigments are mostly concentrated) at the fovea, as observed for nonmyopic eyes, seems to be confirmed in highly myopic eyes as well.

One interesting finding of this study was the absence of RVPs, which were observed in none of the cases. This could be secondary to the high prevalence, in highly myopic eyes, of LHEP, which reportedly should have scarce contractile properties and thus cause limited tangential traction [20, 25]. Another explanation could be that the autofluorescent signal stemming from the RPE in highly myopic eyes is somewhat weaker because of RPE alterations secondary to myopic global expansion. These alterations could make subtle local variations of the B-FAF signal (for example, the relatively brighter signal of RVPs in comparison to nearby areas) undetectable. A third hypothesis is that the displacement of the retinal vessels in myopic eyes might progress so slowly to make undetectable the change in the characteristics of the fluorophores in the areas previously shielded by the retinal vessels and then exposed. The long time required for these small displacements to occur would make the fluorophores of the shielded areas gradually similar to those of the adjacent cells exposed to light, leaving no clue of retinal vessel displacement [26].

The limitations of this study include its retrospective nature, the relatively restricted number of patients, and the variable duration of follow-up. The strengths include the use of an OCT device that can record serial images at the same location, the mean length of the follow-up, and the use of B-FAF and SD-OCT to study LMHs.

To conclude, we show that LMHs in the eyes with PM differ from LMHs in nonmyopic eyes in the greater presence of LHEP, the higher rate of evolution towards FTMH, and the absence of RVPs. Standard ERMs and LHEPs are found in more than 90 and 75% of cases, respectively, and in approximately two-thirds of cases, a standard ERM and LHEP coexist. Similarly to LMHs in nonmyopic eyes, the majority of LMHs in the eyes with PM show substantial stability of BCVA and the anatomic parameters evaluated with B-FAF and SD-OCT over years-long follow-up periods.

Compliance with ethical standards

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

Ethical approval All procedures were in accordance with the ethical standards of the institutional research committee (Institutional Review Board of the University of Molise) and with the 1964 Helsinki declaration and its later amendments.

Informed consent For this type of study, formal consent is not required.

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