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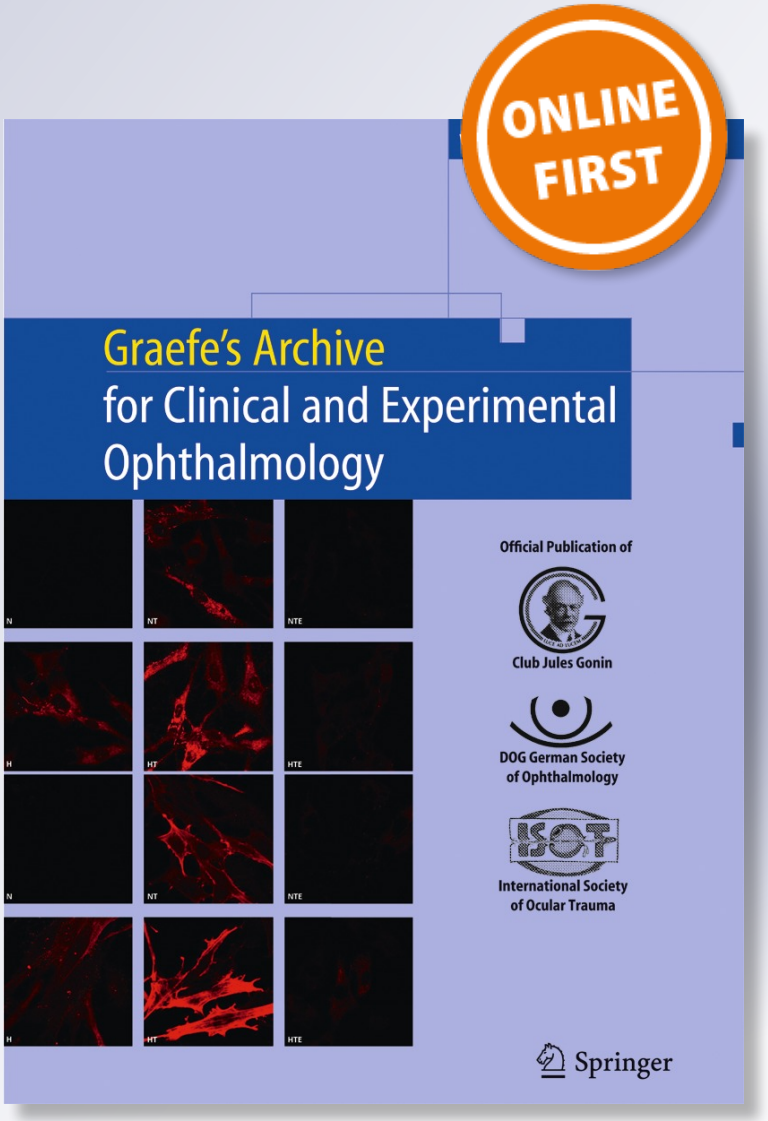

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RETINAL DISORDERS

Lamellar macular hole in high myopic eyes with posterior staphyloma: morphological and functional characteristics

Frisina Rino [1] · Zampedri Elena [1] · Marchesoni Ivan [1] · Bosio Paolo [1] · Parolini Barbara [2] · Romanelli Federica [1]

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Abstract
Purpose To study morphological and functional characteristics of myopic lamellar macular hole (LMH) with posterior staphyloma.
Methods Retrospective observational longitudinal study. Forty myopic eyes affected by LMH and posterior staphyloma have been examined. Pathological myopia was defined as axial length equal or superior to 26.5 mm. LMH was defined on the basis of the following characteristics: irregular foveal contour, inner retinal defect with or without intraretinal splitting and absence of full thickness retinal defect. Demographic and functional parameters were: age, sex, status of lens and best corrected visual acuity (BCVA). Tomographic parameters were: type of LMH, macular retinoschisis (MRS), posterior vitreous detachment (PVD), type of epiretinal membrane (ERM), integrity of ellipsoid zone (EZ) and external limiting membrane (ELM), residual foveal thickness (RFT) and maximal diameter of intraretinal splitting (MDIRS).
Results The statistical analysis showed a significant prevalence of posterior vitreous adherence in the atypical ERM subgroup ($P=0.001$). EZ ($P=0.006$) and ELM ($P=0.007$) damages were significantly associated with the atypical ERM subgroup. RFT was statistically lower in the atypical ERM subgroup compared to the conventional ERM subgroup ($P=0.015$). During the follow-up, the statistical analysis showed a significant reduction of RFT in the atypical ERM subgroup ($P=0.041$).
Conclusions Myopic lamellar macular hole (LMH) associated with atypical ERM is a more severe clinical entity than myopic LMH associated with conventional ERM.

Keywords Lamellar macular hole · Epiretinal membrane · Macular retinoschisis · Posterior vitreous detachment · Myopic traction maculopathy · Ellipsoid zone

Introduction

Lamellar macular hole (LMH) is a distinct clinical entity characterized by an irregular foveal contour, a break in the inner fovea, intraretinal splitting and an intact foveal photoreceptor [1]. In contrast, some authors recently reported that some types of idiopathic LMH were characterized by outer retinal layers, an external limiting membrane (ELM) and ellipsoid zone (EZ) disruption [2–8].

Several articles have described an epiretinal membrane (ERM) associated with idiopathic LMH, proposing the following two types: conventional ERM characterized by tractional properties, and atypical ERM characterized by a greater thickness than conventional ERM and without tractional properties. In literature, the latter is called different names: 'thickened', 'dense', 'epiretinal proliferation' and 'atypical' ERM [1, 5–7]. A common agreement on the tractional pathogenesis of LMH associated with conventional ERM is accepted, while the pathogenesis of LMH associated with atypical ERM is still debated. Recently, two hypotheses have been proposed: one based on the remodeling processes within the vitreous cortex supported by the persistence of posterior vitreous adherence [5], the second based on the Müller cell proliferation

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supported by an immunohistological finding of glial fibrillary acidic protein positive cells in atypical ERM [5]. Moreover, different histological compositions of the two types of ERM have been shown. Atypical ERM is composed of abundant clusters of fibrous, long-spacing collagen embedded in compactly folded, native vitreous collagen strands; conventional ERM is composed of anti-alfa-smooth muscle actin that probably confers distinctive contractive properties [5]. Although these findings did not enable clarification of the pathogenesis of atypical ERM, they lead to the hypothesis that atypical ERM is a different clinical entity from conventional ERM. Despite the presence of several articles about idiopathic LMH with associated ERMs, only few papers about LMH associated with high myopia and none about myopic LMH with associated ERMs have been published so far.

Purpose

To study morphological and functional characteristics of myopic LMH with posterior staphyloma.

Design

Retrospective observational longitudinal study.

Methods

The clinical charts of patients affected by LMH associated with pathological myopia and posterior staphyloma have been recruited from the database of the Department of Ophthalmology of Santa Chiara Hospital of Trento, Italy, from January 2010 to March 2015. The corresponding optical coherence tomography (OCT) examinations from the database of high-resolution spectral domain OCT (HR SD OCT; Cirrus OCT Carl Zeiss Meditec, Inc., Dublin, CA, USA) have been analyzed. OCT scan images of each patient at the time of diagnosis, between 12 and 18 months, and after 24 months (range 24–60 months) were analyzed for evaluating LMH evolution. In December 2014, all patients were contacted by telephone and invited to undergo ophthalmoscopic examination, ultrasound (US) and OCT studies. Only those that accepted were recruited for our study.

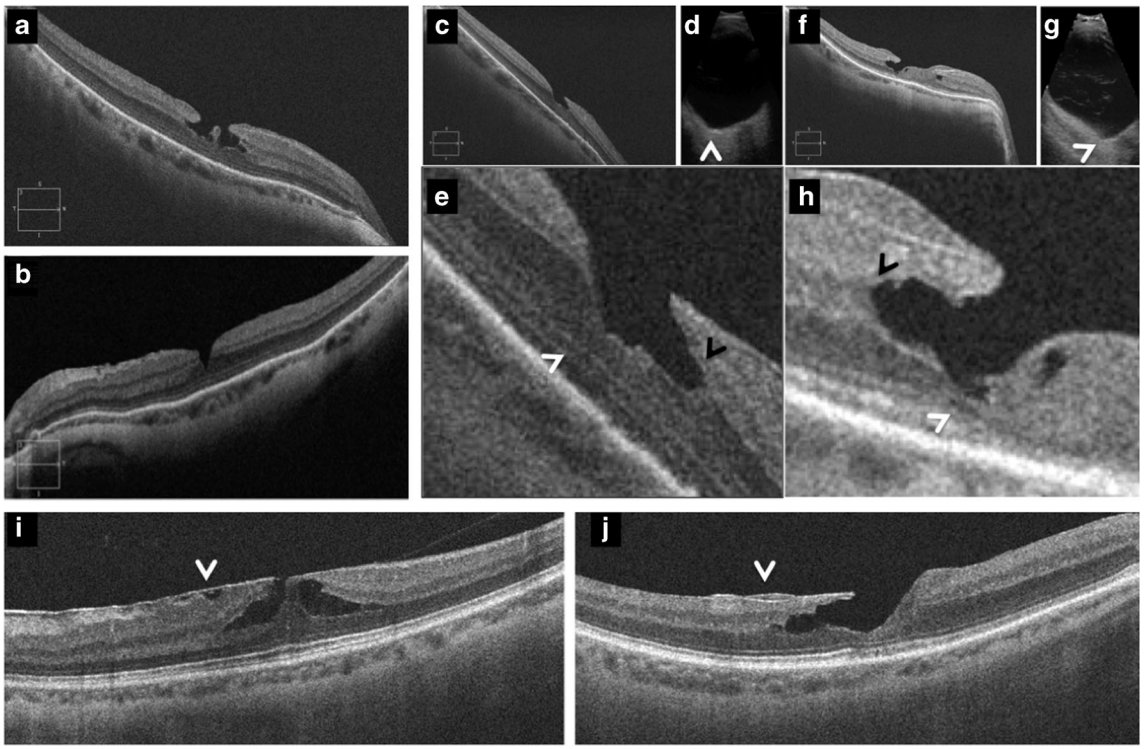

Fig. 1 **a**: LMH with intraretinal splitting (IR SPLIT LMH). **b**: LMH V shaped (V LMH). **c**–**e**: LMH (**c**: OCT scan image) with posterior staphyloma type II (*white arrow*) (**d**: US scan image) characterized by an irregular foveal contour, intraretinal splitting (*black arrow*), and an inner fovea defect with integrity of ELM and EZ (*white arrow*) (**e**: magnification of OCT scan image). **f**–**h**: LMH (**f**: OCT scan image) with posterior staphyloma type I (*white arrow*) (**g**: US scan image) characterized by irregular foveal contour, intraretinal splitting (*black arrow*) and inner fovea defect with ELM and EZ interrupted (*white arrow*) (**h**: magnification of OCT scan image). **i**: LMH with conventional ERM (*white arrow*). **j**: LMH with atypical ERM (*white arrow*)

Every case without follow-up or with incomplete data was excluded. The authors excluded every case of myopic LMH associated with metabolic and vascular pathologies, and every case with previous history of bulbar trauma and vitreoretinal surgery. For patients that underwent vitreoretinal or cataract surgery after the recruitment date, we considered the follow-up until the surgery date. Pathological myopia was defined as axial length (AL) equal or superior to 26.5 mm [9].

Posterior staphyloma was defined according to Curtin's classification. Horizontal and vertical axial B scans were performed to confirm the type of posterior staphyloma.

LMH was defined according to Witkin's diagnostic criteria [1]:

- irregular foveal contour
- break in the inner fovea
- intraretinal splitting
- intact foveal photoreceptor

Moreover, two important changes to the Witkin's criteria were reported.

Firstly, we arbitrarily distinguished two morphological types of LMH based on our observation of the morphology of LMH:

- LMH intraretinal splitting (IR split LMH) was characterized by a separation in the inner layers of the intraretinal tissue adjacent to the hole and extended from one side only: temporally or nasally or on both sides, as described by Witkin (Fig. 1a).
- LMH V-shaped (V LMH) was characterized by a tissue defect with a 'V' configuration due to the vertical slope of LMH walls converging towards the outer layers (Fig. 1b). The involvement of the outer retinal layers distinguishes V LMH from macular pseudo-hole (MPH). The last one is characterized by an irregular foveal contour with intact retinal layers.

Finally, in light of the recent knowledge on the involvement of the outer retinal layers in the LMH [2–8], we evaluated the integrity of the outer retinal layers relying on the continuity of hyper-reflective lines corresponding to EZ and ELM in the foveal area shown by OCT (Fig. 1c–h).

The scans of LMH were the following for each case:

- Macular cube 512 × 128: from the macular cube 512 × 128 scan analysis, advanced visualization displays cross section of the image cube through three dimensions.
- 5 HD Line raster: 5 lines of 6 mm of length, 250 μm of spacing. Each of the five lines was scanned four times and with selective pixel profiling, the optimal image was displayed.

The clinical parameters recorded were the following:
Demographic parameters:

- age (years)
- sex: male (M) or female (F)
- eye involved: right (R) or left (L)
- status of lens: phakic (P), pseudophakic (PP), aphakic (AP)

Functional parameters:

- best corrected visual acuity (BCVA) converted from Snellen to logarithm of the minimum angle of resolution (LogMAR)

Ultrasound parameters:

- AL measurement by hand-held applanation of US (A-scan US). The measurements were performed by automatic freeze. Measurements were accepted as valid if the values that were almost similar for three consecutive scans with a difference not exceeding 0.5 mm

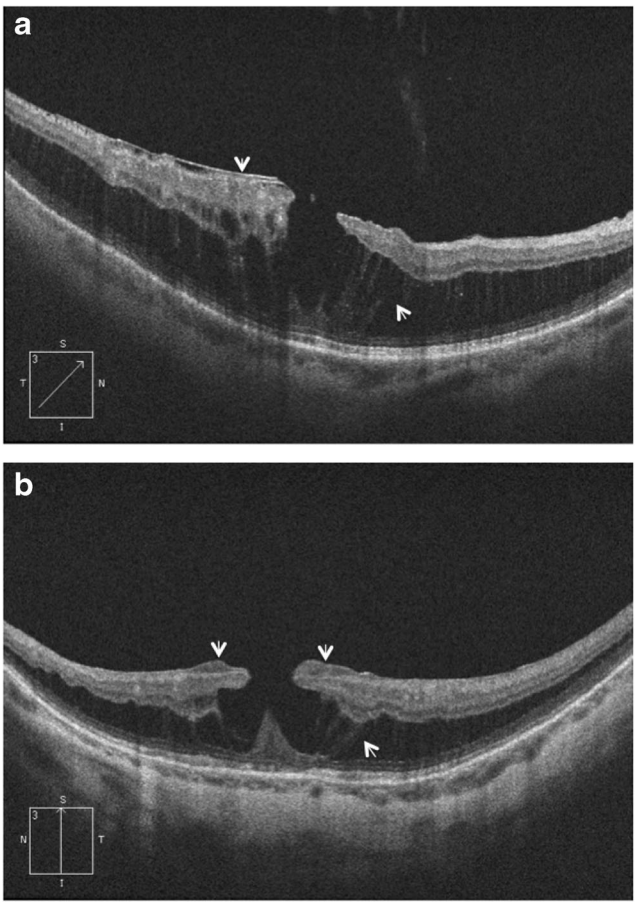

Fig. 2 **a**. LMH with macular retinoschisis associated with conventional ERM (*white arrows*). **b**. LMH with atypical ERM (*white arrows*)

Tomographic parameters:

- LMH type (IR split LMH or V LMH)
- ERM type: ERM type was defined according to the recent findings of ERM associated with LMH by Schumann [7] and were the following:

– Conventional ERM is characterized by a highly reflective line adjacent and overlying the retinal nerve fiber layer (RNFL; Fig. 1i).
– Atypical ERM is characterized by a thick membrane delimited by a highly reflective line and filled by moderately reflective material (Fig. 1j).

- Macular retinoschisis (MRS): MRS is a pathological disorder associated with high myopia, characterized by intraretinal splitting of the outer and inner retinal layers with dense columnar structures in the macular area, defined by Duker as perpendicular strands (which may represent stretched Müller cells) that join the inner and outer retinal layers [9]. We compared the functional and morphological characteristics between the subgroup of LMH associated with MRS (LMH MRS subgroup) and the subgroup of LMH not associated with MRS (LMH NO MRS subgroup). Figure 2 shows LMH with the two types of ERM associated with MRS.
- EZ and ELM integrity

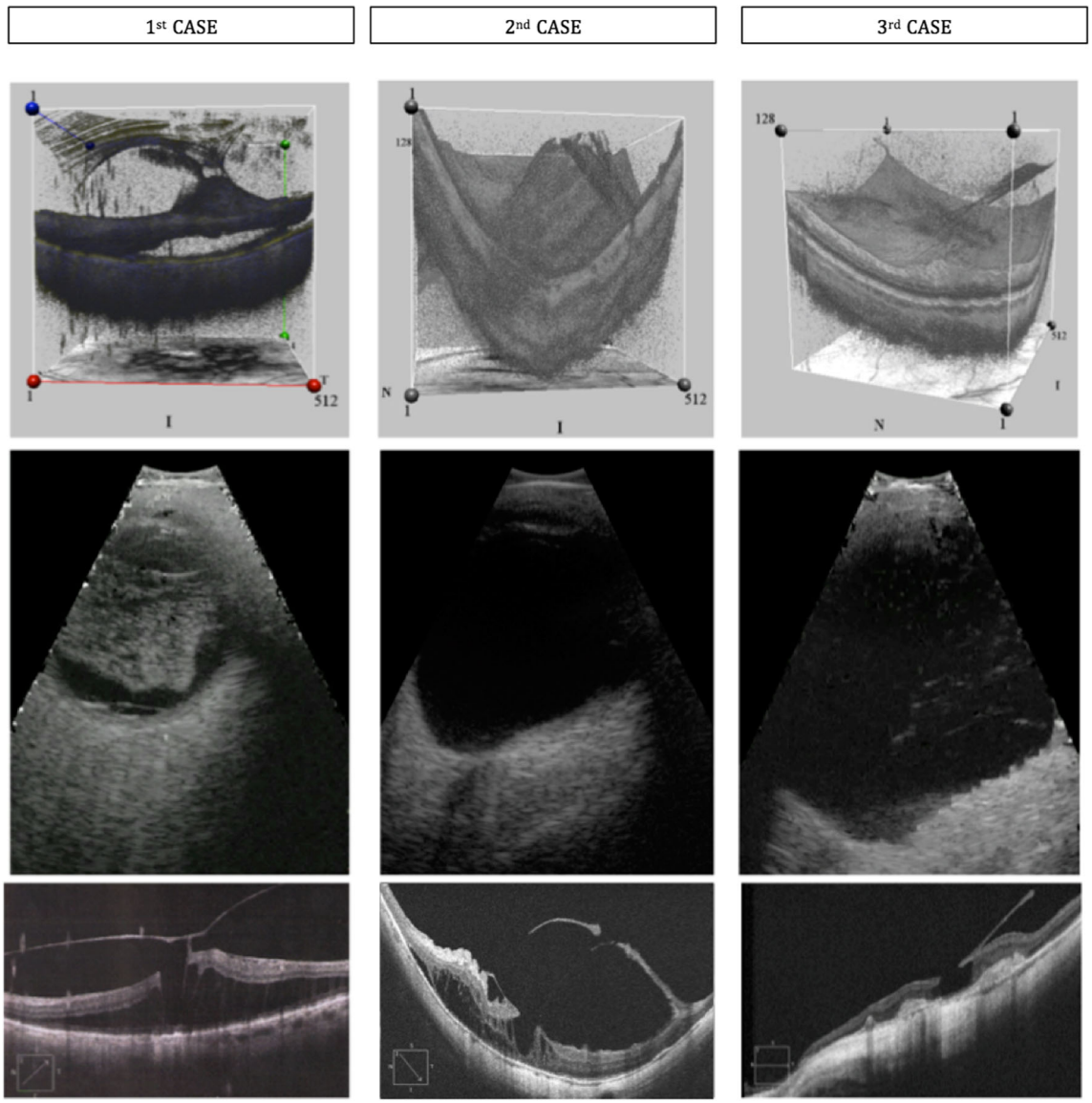

Fig. 3 1st case: Myopic LMH with posterior staphyloma II, MRS and synchysis scintillans. 2nd case: Myopic LMH with posterior staphyloma type I, MRS. 3rd case: Myopic LMH associated with posterior staphyloma type I characterized by atypical ERM

- Posterior vitreous detachment (PVD): PVD was evaluated by displaying a 3D cube macular 512 × 128 of HR SD OCT. The authors were able to see only PVD in the macular region and not the relations between the vitreous and peripheral retina (Fig. 3).
- Residual foveal thickness (RFT) and maximal diameter of intraretinal splitting (MDIRS): RFT and MDIRS were, respectively, the greatest thinning point of the retinal tissue inside the LMH and the maximal diameter of intraretinal splitting. They were measured in micrometers (μm) by caliber of OCT. MDIRS was measured only in the IR split LMH subgroup; the absence of intraretinal splitting in V LMH did not allow measurement of the MDIRS.

The comparison of BCVA, RFT and MDIRS changes at the different time points of follow-up, between the two subgroups of ERM types, the two subgroups of LMH type and between the subgroup of LMH with MRS and without MRS were analyzed. The incidence of FTMH during the follow up was evaluated.

Statistical analysis

SPSS Software version 22.0 (IBM Corporation, New York, NY, USA) for statistical analysis of the data was computed. The statistical comparison of quantitative parameters between the subgroups of ERM type and subgroups of LMH type (age, sex, BCVA, RFT and MDIRS) was performed by U Mann–Whitney test. The association of qualitative parameters (gender, lens status, LMH type, PVD, integrity of EZ and ELM) with the type of ERM and the type of LMH was calculated using Pearson's chi-square test. The comparison of BCVA, RFT and MDIRS at the different time points of follow-up between the two subgroups of ERM types and between the subgroup of LMH with MRS and without MRS was determined using a Wilcoxon test. A $P < 0.05$ was considered to be statistically significant.

Results

Forty eyes of 38 patients, 16 (40 %) males and 22 (60 %) females, affected by LMH associated with high myopia and posterior staphyloma were recruited. The mean follow-up was 45 months (range 24 to 72 months).

All eyes were affected by posterior staphyloma involving the macular area. Nineteen eyes were affected by posterior staphyloma type I, 21 eyes by posterior staphyloma type II. In all eyes, LMH was associated with ERM.

Baseline clinical (demographic and functional) and morphological data of LMH type subgroups, ERM type subgroups and the whole group of LMH are reported in Tables 1 and 2.

Table 1 Baseline demographic and functional parameters of whole myopic LMH group, LMH type subgroups and ERM type associated with LMH subgroups

Baseline demographic and functional parameters of whole myopic LMH group						
Whole group ERM	No. of eyes (no. of patients)	Age* years mean - ST DV (range)	Sex† female/male no. of patients (%)	Eye† right/left no. (%)	Lens† phakic/Pseudophakic no. (%)	BCVA* LogMar mean - ST DV (range)
	40 (38)	71.23 ± 11.04 (44–94)	22 (57.89)/16 (42.1)	20 (50)/20 (50)	18 (45)/22 (55)	0.43 ± 0.33 (0–1)
Baseline demographic and functional parameters of IR split and V shaped LMH subgroups						
LMH type	No. of eyes (%) (no. of patients)	Age* years mean - ST DV (range)	Sex† female/male no. of patients (%)	Eye† right/left no. (%)	Lens† phakic/Pseudophakic no. (%)	BCVA* LogMar mean - ST DV
IR split	31 (77.5) (29)	71.3 ± 11.03 (44–94)	17 (58.62)/12 (41.38)	16 (51.61)/15 (48.39)	15 (48.38)/16 (51.61)	0.46 ± 0.36 (0–1)
V shaped	9 (22.5) (9)	72.5 ± 9.68 (59–82)	5 (55.5)/4 (44.5)	4 (44.5)/5 (55.5)	3 (33.3)/6 (66.7)	0.33 ± 0.25 (0–0.7)
p value	*0.476*	*0.254*	*0.633*	*0.721*	*0.375*	
Baseline demographic and functional parameters of conventional and atypical ERM subgroups						
ERM type	No. of eyes (%) (no. of patients)	Age* years mean - ST DV (range)	Sex† female/male no. of patients (%)	Eye† right/left no. (%)	Lens† phakic/Pseudophakic no. (%)	BCVA* LogMar mean - ST DV (range)
Conventional ERM	23 (57.5) (23)	70.05 ± 12.10 (44–94)	16 (69.57)/7 (30.43)	10 (43.48)/13 (56.52)	15 (65.2)/8 (34.8)	0.38 ± 0.34 (0–1)
Atypical ERM	17 (42.5) (15)	72.67 ± 9.71 (59–86)	6 (40)/9 (60)	10 (58.82)/7 (41.18)	3 (17.64)/14 (82.36)	0.50 ± 0.32 (0–1)
p value	*0.540*	*0.069*	*0.324*	*0.003*‡	*0.171*	

* U Mann–Whitney test

† Pearson's chi-squared test

‡ significant

Table 2 Baseline morphological parameters of the whole group of myopic LMH, LMH type subgroups and ERM type associated with LMH subgroups

Baseline morphological parameters of whole group of myopic LMH									
Whole group myopic LMH	No.(%)	AL mm mean – ST DEV (range)	RFT* μm mean - ST DEV (range)	MDIRS* μm mean - ST DEV (range)	MRS yes/no no. (%)	PVD† yes/no no. (%) [not evaluable]	EZ† Intact/not intact no. (%) [not evaluable]	ELM† Intact/not intact no. (%) [not evaluable]	
	40	29.6 ± 1.4 (27.3–32.5)	109.17 ± 47.01	685.58 ± 363.06	10 (25)/30 (75)	28 (70)/11 (27.5) [1] (2.5)	19 (47.5)/20 (50) [1] (2.5)	22 (55) [1] (2.5)/17 (42.5)	
Baseline morphological parameters of IR split and V LMH subgroups									
ERM type	No. (%)	ERM Type conventional/ atypical no. (%) [not evaluable]	AL mm mean – ST DEV (range)	RFT* μm mean - ST DEV (range)	MDIRS* μm mean - ST DEV (range) [measured in IR split LMH no. of cases: 31]	MRS yes/no no. (%)	PVD† yes/no no. (%) [not evaluable]	EZ† Intact/No Intact no. (%) [not evaluable]	ELM† Intact/No Intact no. (%) [not evaluable]
IR split LMH	31 (77.5)	19 (61.29)/12 (38.71)	30.01 ± 2.4 (28.79–32.5)	107.32 ± 45.78 (34–185)	777.13 ± 361.67 (202–1719)	9 (29)/22 (71)	22 (70.97)/8 (25.81) [1] (3.22)	14 (45.16)/17 (54.84)	17 (54.84)/14 (45.16)
V LMH	9 (22.5)	4 (44.45)/5 (55.56)	29.1 ± 1.7 (27.9–31.9)	131.88 ± 48.27 (61–220)	[not evaluable]	1 (11.1)/8 (88–9)	6 (66.67)/3 (33.33)	5 (55.5)/3 (33.3) [1] (11.1)	5 (55.5)/3 (33.3) [1] (11.1)
P value	–	*0.6574*	*0.7632*	–	*0.865*	*0.3552*	*0.4621*	*0.4621*	
Baseline morphological parameters of conventional and atypical ERM subgroups									
LMH type	No. (%)	LMH TYPE IR split/V shaped no. (%)	AL mm mean – ST DEV (range)	RFT* μm mean - ST DEV (range)	MDIRS* μm mean - ST DEV (range)	MRS yes/no no. (%)	PVD† yes/no no. (%) [not evaluable]	EZ† Intact/No Intact no. (%) [not evaluable]	ELM† Intact/No Intact no. (%) [not evaluable]
Conventional ERM	23 (57.5)	19 (82.61)/4 (17.39)	29.3 ± 2.1 (27.3–32.1)	124.77 ± 44.26 (47–185)	679.64 ± 395.25 (202–1719)	5 (21.7)/18 (78.3)	21 (91.3)/2 (8.7)	15 (65.22)/7 (30.43) [1] (4.35)	17 (73.91)/5 (21.74) [1] (4.35)
Atypical ERM	17 (42.5)	12 (70.59)/5 (29.41)	30.2 ± 1.7 (29.8–31.9)	90.11 ± 44.18 (34–220)	692.83 ± 330.61 (352–1539)	5 (29.4)/12 (70.6)	7 (41.17) /9 (52.94) [1] (5.88)	4 (23.53)/13 (76.47)	4 (23.53)/13 (76.47)
P value	–	*0.7724*	*0.015*‡	*0.664*	*0.714*	*0.001*‡	*0.006*‡	*0.007*‡	

* U Mann–Whitney test

† Pearson's chi-squared test

‡ significant

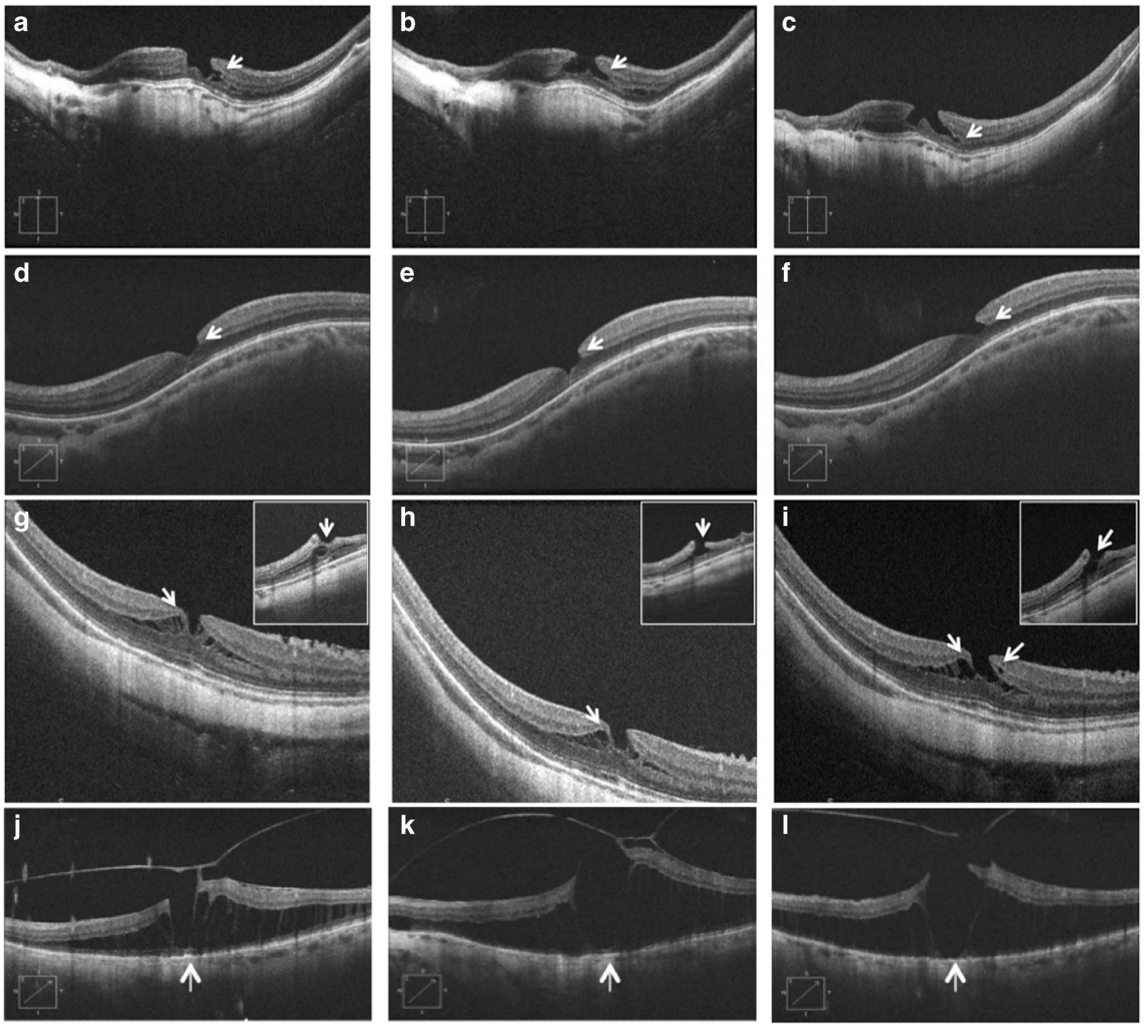

Fig. 4 **a**–**c**: LMH associated with dome shape (**a**), pictures b and c show the morphological changes of LMH with an increase of intraretinal splitting (*white arrows*). **d**–**f**: V LMH associated with posterior staphyloma (**d**), pictures e and f show the morphological changes of V LMH with development of intraretinal splitting (**e**, **f**). **g**–**i**: the increase of MDIRS in LMH with conventional ERM. The three left top images show the evolution of extrafoveal vitreoretinal traction. **j**–**l**: the evolution of LMH with MRS to FTMH (*white arrows*)

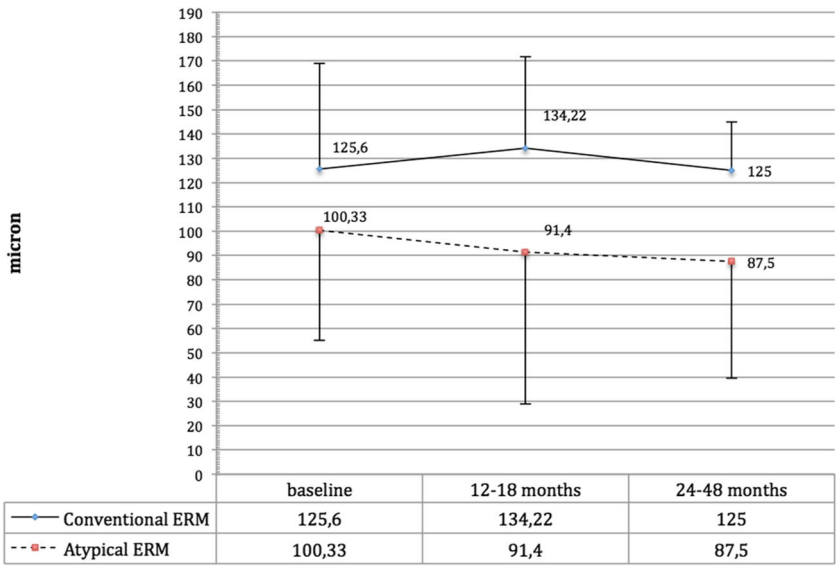

Fig. 5 Trend of RFT changes in the ERM type subgroups of myopic LMH during the follow-up

LMH type: IR split and V shaped LMH

There was no statistical difference of qualitative and quantitative parameters between the two subgroups of LMH type. During the follow up, two cases with V LMH developed an intraretinal splitting in the temporal side (Fig. 4d–f). The statistical analysis of the changes of BCVA, RFT and MDIRS at the different points of follow-up did not show any significant difference.

ERM type: conventional and atypical ERM associated with LMH

The comparison of demographic and functional parameters between the two ERM type subgroups did not show any significant difference, except for the higher prevalence of the pseudophakia condition in the atypical ERM subgroup. However, a statistically significant difference emerged from the comparison of the morphological parameters between the two subgroups. EZ ($P=0.006$) and ELM ($P=0.007$) damages were significantly associated with the atypical ERM subgroup. RFT was statistically lower in the atypical ERM subgroup compared to the conventional ERM subgroup (U Mann–Whitney test $P=0.015$). PVD was prevalent in the conventional ERM subgroup (21 of 23 cases, 91.3 %) compared to the atypical ERM subgroup (7 of 17 cases, 41.17 %; $P=0.001$). During the follow-up, the statistical analysis showed a significant reduction of RFT in the atypical ERM subgroup compared to the conventional ERM subgroup ($P=0.0$; Fig. 5).

MRS associated with LMH

MRS was associated in 5 of 23 cases (21.7 %) of the conventional ERM subgroup and in 5 of 17 cases (29.4 %) of the atypical ERM subgroup. BCVA was worse in the LMH MRS subgroup compared to the LMH NO MRS subgroup (Fig. 6). MDIRS was wider in the LMH MRS subgroup compared to the LMH NO MRS subgroup. One case of LMH associated with MRS developed FTMH after 24 months (Fig. 4j–l).

Discussion

This study showed that myopic LMH with posterior staphyloma progresses during the lifetime of a patient. In 2011, Tanaka published the most recent study about the natural evolution of LMH in high myopia [10]. LMH was considered as a stable condition that rarely progresses to FTMH [10]. Tanaka et al. reported that 17 of 24 myopic eyes affected by LMH (70.83 %) were associated with ERM; however, the characteristics of ERM had not been described [10]. In our series, we found that ERM was always associated with LMH. Furthermore, we have distinguished the type of ERM according to the most recent findings published in literature: conventional and atypical ERM [1, 4–6] (Fig. 1i, j). Significant reduction of RFT in the atypical ERM subgroup with a greater involvement of the outer retinal layers was highlighted, contrasting with the previous hypothesis that LMH is stable over time [9]. Our observations are in accordance with more recent studies demonstrating the involvement of outer retinal layers

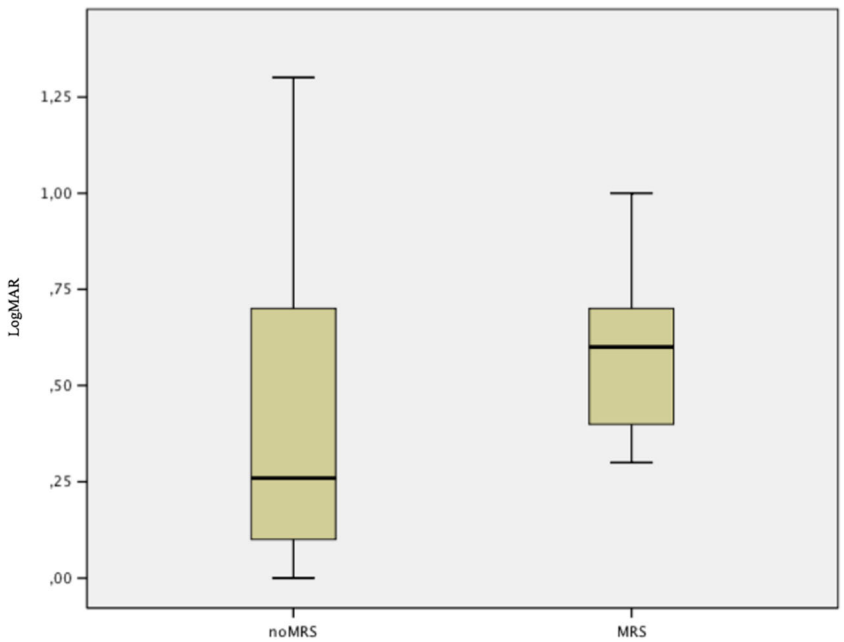

Fig. 6 Boxplot of comparison of BCVA between subgroups of LMH associated or not with MRS

and RFT reduction in idiopathic LMH associated with atypical ERM [5–8].

The significant prevalence of posterior vitreous adherence in the atypical ERM subgroup, discovered in our study, and the recent findings of the presence of vitreous collagen in the histological composition of atypical ERM associated with idiopathic LMH [5–8] are evidence suggesting that the vitreous could play an important role in the pathogenesis of LMH.

The comparison between the IR split LMH subgroup and the V LMH subgroup did not show significant statistic results. The attempt to show that the two morphological types of LMH, commonly encountered in clinical practice, are two different entities did not have a statistical confirmation. We also have reported two cases of V LMH that become IR split LMH during the follow-up. This leads us to assume that these two morphological shapes of LMH are expression of the same pathology. It remains unclear why some LMHs start and progress in more depth, as V LMH, and other more in extension, as IR split LMH.

In our series, although only one case of LMH associated with MRS developed FTMH, similar to Tanaka's study, a higher trend of deterioration over time, due to an increase of MDIRS and a reduction of RFT in whole group of myopic LMH, was discovered. Some examples of the morphological changes of LMH during the follow-up are reported in Fig. 4 (Figure 4a–c, g–i). MRS is the most frequent complication of myopic traction maculopathy (MTM) [11–20]. Several authors have studied the natural evolution of MRS showing various incidences of LMH: from 4.8 to 20.7 % [14, 18]. Sun, in 2010, described the natural evolution of MRS to FTMH in high myopia, highlighting an intermediate phase characterized by the formation of LMH [21]. Although the group of patients is small and it is necessary to perform additional studies on a larger number of cases, the findings reported in literature and our experience make us believe that macular retinoschisis could contribute to the worsening of LMH and to the evolution towards FTMH over time. In conclusion, according to our findings, we can assert that myopic LMH associated with atypical ERM is a more severe entity than myopic LMH associated with conventional ERM and it is not a stable condition.

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Compliance with ethical standards

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.

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

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