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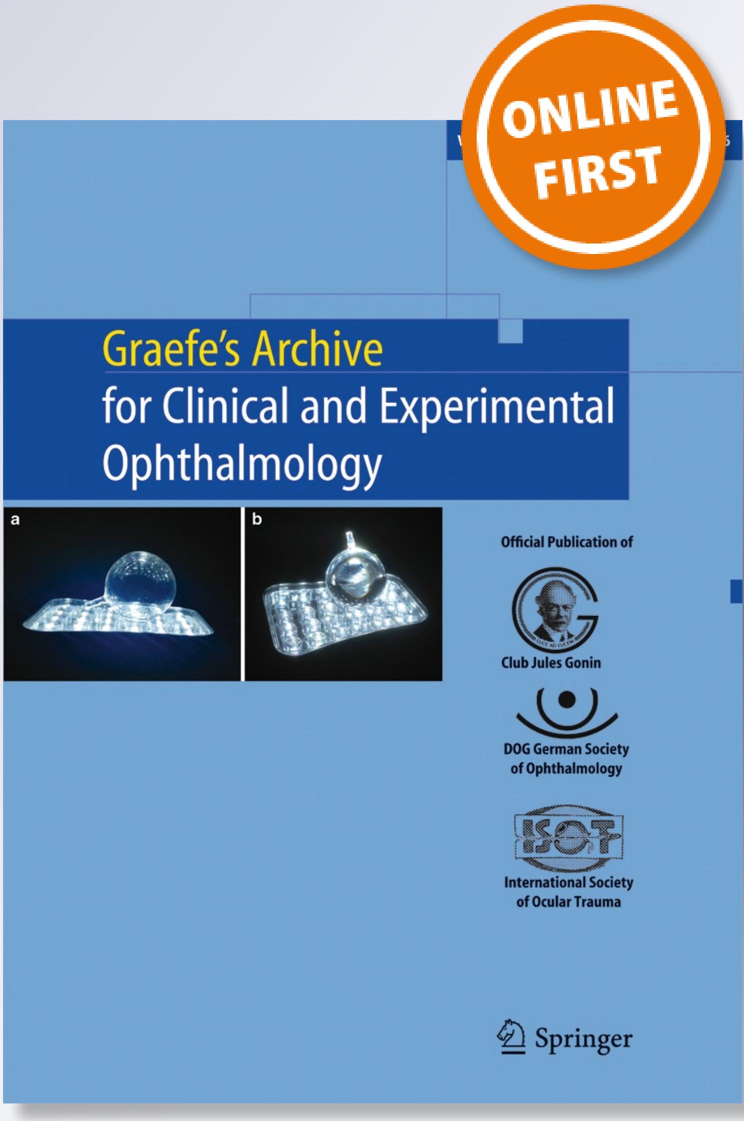

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RETINAL DISORDERS

Spectral-domain optical coherence tomography findings in idiopathic lamellar macular hole

Elena Zampedri[1] · Federica Romanelli[1] · Francesco Semeraro[2] · Barbara Parolini[3] · Rino Frisina[1]

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Abstract
Background To evaluate demographic, functional, and morphological parameters of idiopathic lamellar macular hole (ILMH).
Methods Observational longitudinal retrospective study.

Optical coherence tomography examinations and corresponding clinical charts of a series of consecutive patients affected by ILMH, between January 2010 and March 2015, from the database of the Department of Ophthalmology of Trento Hospital, Italy, have been collected and examined.

Demographic and functional parameters were: age (year), gender (male/female), eye (right/left), lens status, best-corrected visual acuity (BCVA) in logarithm of the minimum angle of resolution (LogMAR).

Tomographic parameters were: LMH shape pattern (intraretinal splitting LMH, IR split LMH, and V-shaped LMH, V LMH), posterior vitreous detachment (PVD yes/PVD no), ERM type (conventional ERM and atypical ERM), integrity of ellipsoid zone (EZ) and external limiting membrane (ELM), residual foveal thickness (RFT) micron (μ), maximal diameter of intraretinal splitting (MDIRS) (μ).
Results One hundred and eighty-nine eyes of 175 patients were included. The mean age was 72.84 ± 9.6, range 41–96 years. BCVA mean was 0.24 ± 0.25, range 0 –1.3 LogMAR. One hundred and forty-one eyes (74.6 %) were affected by IR split LMH, 48 eyes (25.4 %) were affected by V LMH. Every cases of ILMH were associated with ERM: 117 (61.9 %) conventional ERM, 72 (38.1 %) atypical ERM. A significant prevalence of female gender, phakic condition, and PVD in conventional ERM ILMH subgroup ($P = 0.000$) was found. BCVA mean was better in the conventional ERM ILMH subgroup ($P = 0.000$). An association between the interruption of the outer retinal layers (EZ and ELM) and atypical ERM ILMH subgroup was highlighted ($P = 0.000$). The statistical analysis showed a correlation between BCVA and integrity of ELM ($P = 0.000$). RFT significantly decreased in atypical ERM ILMH subgroup at 24 months compared to time point 0 ($P = 0.027$). A progressive increase of MDIRS in both subgroups at 12 months and in atypical ERM ILMH subgroup at 24 months ($P = 0.007$) was highlighted.
Conclusions This study demonstrated that ILMH was not a stable condition, showing morphological changes and an involvement of the outer retinal layers during the 2 years of follow-up.

Keywords Lamellar macular hole · Epiretinal membrane · Ellipsoid zone · External limiting membrane · Posterior vitreous detachment · Optical coherence tomography

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Introduction

In the last 10 years, the evolution of optical coherence tomography (OCT) has allowed several authors to describe the morphological characteristics of idiopathic lamellar macular hole (ILMH) and to develop knowledge on this pathology. However, there are some issues that have not been fully clarified yet and others that have not been investigated.

Firstly, the morphological aspects of epiretinal membrane (ERM) associated with ILMH, have been recently the most debated topics. From 2006, when Witkin proposed the diagnostic criteria of ILMH, to 2016, several authors have defined the two ERM types associated with ILMH confirming the different characteristics of both [1–6]. One is characterized by tractional properties with stretched intraretinal layers representing the mean cause of macular pucker; this is called in literature 'conventional or tractional ERM'. The other one appears much thicker at the OCT, with a moderate internal reflectivity delimited by an outside line with high hyperreflectivity. This type of ERM follows retinal surface without altering the retinal profile and without signs of intraretinal tissue traction. Although the pathogenesis of this specific type of ERM is not known, the close relationship of this ERM with retinal tissue and vitreous body emerged from immunohistochemical studies, permitting some authors to make two different hypotheses. One is based on the remodelling process within the vitreous cortex supported by the finding of native vitreous collagen in the composition of ERM, the other one based on the glial cell proliferation supported by the immunohistochemical positivity to glial cells in the composition of ERM [3–9]. This type of ERM is called by different names: dense, thickened, epiretinal proliferation, degenerative and atypical [1, 3, 5, 7]. The heterogeneity of the names given to this ERM type is an indication that a unique and shared definition of ERM associated with ILMH has not yet been established. Regardless of the different names by which this ERM type has been defined in the literature, appropriate to everyone, but impacted by certain morphological characteristics or by pathogenetic hypothesis, the authors of the current study have adopted generic terms until a shared consensus on terminology is defined : 'atypical' ERM and 'conventional ERM'.

The other two issues are about the diagnostic criteria of ILMH. Witkin in 2006 described the following diagnostic criteria of ILMH: irregular foveal contour, break in the inner fovea, intraretinal split, and intact foveal photoreceptors.

In the current study, the authors adopted the first two of Witkin's criteria but not the last two.

It is common experience to view different types of LMH: some individuals meet all the diagnostic criteria described by Witkin, others are characterized by irregular shape, without intraretinal splitting, not meeting Witkin's diagnostic criteria. Furthermore, although the ILMH is not characterized by full-thickness retinal defect, the authors believe that there could be an involvement of the photoreceptors, the ellipsoid zone (EZ), and the external limiting membrane (ELM).

In this study demographic, functional and morphological parameters of ILMH were evaluated.

Materials and methods

Observational longitudinal retrospective study.

OCT examinations and corresponding clinical charts of a series of consecutive patients affected by ILMH, between January 2010 and March 2015, from the database of high-resolution spectral-domain OCT (HR SD OCT), Cirrus OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA) of the department of the Santa Chiara Hospital at Trento, Italy have been collected and examined.

The analyzed OCT scans, without eye-tracking system, of ILMH were the following for each case:

- Macular cube 512 × 128: from the macular cube 512 × 128 scan analysis, advanced visualization displays a cross-section of the image cube through three dimensions. (Fig. 1)
- 5 HD line raster: five lines of 6 millimeters (mm) in length, 250 micrometers (m) of spacing. Each of the five lines is scanned 4 times, and with selective pixel profiling, the optimal image is displayed. (Fig. 1)

Inclusion criteria

The ILMH was defined according to the following criteria:

- irregular foveal contour
- break in the inner fovea
- inner retinal defect with or without intraretinal splitting
- intact foveal photoreceptors

In the light of Witkin's diagnostic criteria, the authors decided to include all cases analyzed by OCT, characterized by irregular foveal contour and break in the inner fovea. Moreover, all cases with inner retinal defect, regardless of the presence or not of intraretinal splitting, were included, defining the new shape of ILMH, as will be described later. In addition, all cases with no full-thickness defect, regardless of the integrity or not of photoreceptors, were included.

Exclusion criteria

The authors excluded all cases of LMH associated with ERM secondary to:

- metabolic pathologies (diabetes mellitus)
- vascular pathologies
- infectious diseases
- inflammatory pathologies
- previous vitreoretinal surgery
- previous bulbar trauma

Demographic and functional parameters collected from clinical charts were the following: age (year), gender (male/female), eye (right/left), lens status (phakic/

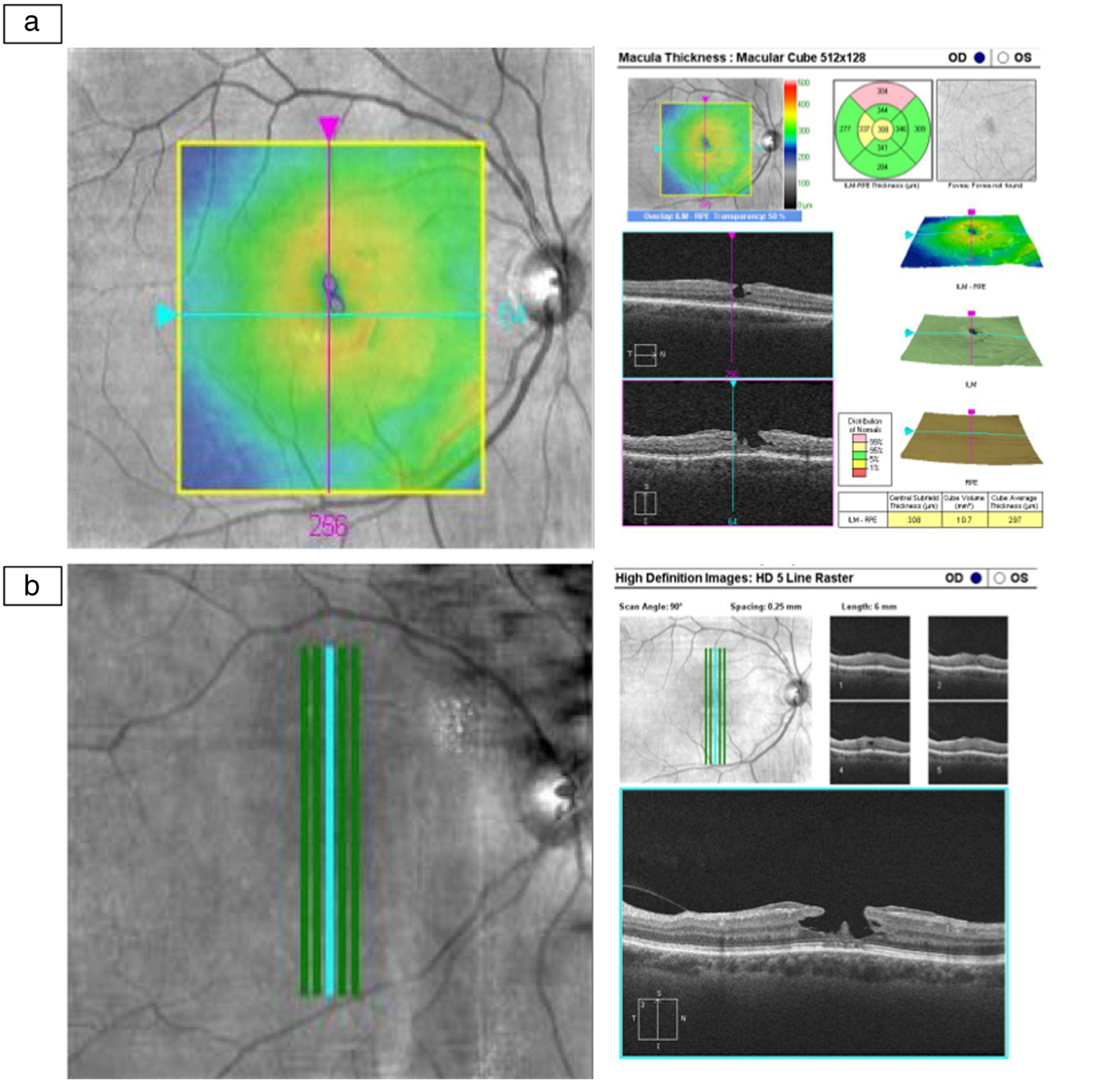

Fig. 1 **a** It shows a macular cube scan 512 × 128. **b**. It shows a 5 HD line raster (5 lines of 6 mm in lenght and 250 micrometers of spacing)

pseudophakic/aphakic), and best-corrected visual acuity (BCVA). BCVA was converted from Snellen chart to logarithm of the minimum angle of resolution (LogMAR).

The tomographic parameters were the following:

Morphological parameters

– LMH shape pattern:

two shape patterns of LMH, according to the presence or not of intraretinal splitting. Intraretinal splitting LMH (IR split LMH) and V-shaped LMH (V LMH) were identified.

- Intraretinal splitting LMH (IR split LMH): LMH characterized by a splitting at the level of outer plexiform layer adjacent to the hole and extended from one side only: temporally or nasally or on both sides (Fig. 2)
- V-shaped LMH: LMH characterized by a tissue defect, 'V' configuration due to the vertical slope of the hole walls which converge towards the outer layers (Fig. 2)

– Posterior vitreous detachment (PVD) (yes/no).

The posterior vitreous detachment was evaluated by displaying 3D macular cube 512x128 of HR SD-OCT. The authors were able to analyze only PVD in macular region and not the relations between the vitreous and peripheral retina (Fig. 3)

– ERM type (conventional ERM/ atypical ERM) (Fig. 4)
– Integrity of EZ (intact/not intact)

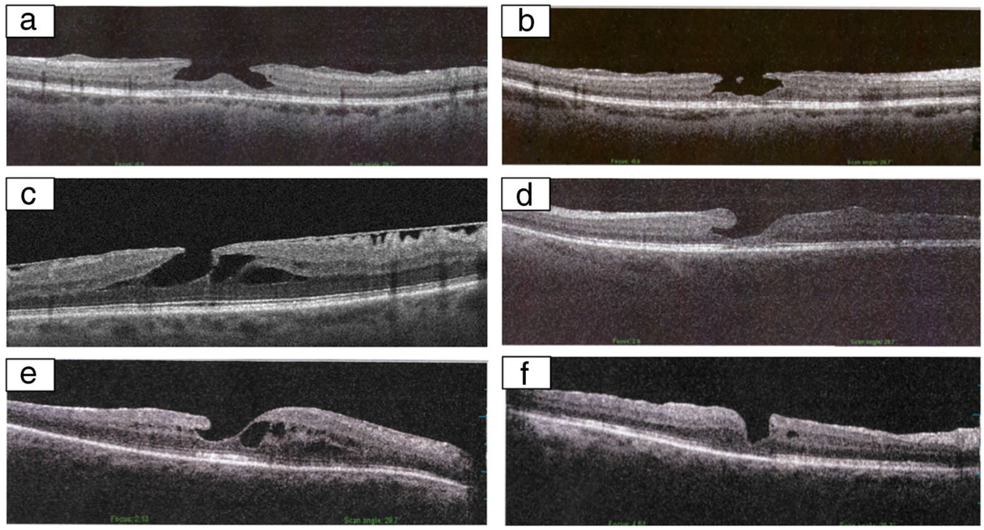

Fig. 2 Different morphological shapes of ILMH. **a** ILMH with intraretinal splitting with omega-shaped configuration. **b** ILMH with intraretinal splitting. **c** ILMH with intraretinal splitting filled with cysts compartmentalized by columns of retinal tissue. **d** ILMH with intraretinal splitting on one side. **e** ILMH with intraretinal splitting on one side and intraretinal cysts on the opposite side. **f** ILMH with V-shaped configuration

– Integrity of ELM (intact/not intact)
  The integrity of the outer layers was evaluated by HR SD-OCT, based on the continuity of hyperreflective lines corresponding to EZ and ELM in the foveal area.

Morphometric parameters

– Residual foveal thickness (RFT) micron (μ)
  The greatest thinning point of the retinal tissue inside the ILMH (Fig. 5)
– Maximal diameter of intraretinal splitting (MDIRS) (μ)
  The maximum size of the intraretinal splitting (Fig. 5) (measured only in IR split LMH and not in V-shaped LMH for the absence of intraretinal splitting).

Statistical analysis

Statistical analysis of the data was computed using SPSS Software Version 22.0 (IBM Corporation, New York, NY, USA).

The distribution of our sample was not normal; as a consequence, we performed non-parametric tests. The difference in the mean age, mean BCVA, mean RFT and mean MDIRS between both ERMs were determined using the Mann–Whitney U test. The association of sex, lens status, LMH type, PVD, integrity of EZ and ELM with the two ERMs were calculated using Pearson's chi-square test. The difference in mean BCVA, mean RFT, mean MDIRS at 0, 12, and 24 months between both ERMs was determined using the Wilcoxon test.

$P < 0.05$ was considered to be statistically significant.

Results

For this study, 189 eyes, 86 right (45.5 %) and 103 left (54.5 %), of 175 patients, 114 (65.1 %) female and 61 (34.9 %) male,were included. The mean age was 72.84 ± 9.6, range 41–96. One hundred and thirty-one eyes (69.3 %) were phakic and 58 (30.7 %) were pseudophakic. The mean BCVA was 0.24 ± 0.25, range 0–1.3 LogMAR. (Table 1)

Tomographic parameters

One hundred and forty-one eyes (74.6 %) were affected by IR split LMH, 48 eyes (25.4 %) were affected by V LMH. PVD was present in 129 of 183 eyes (70.5 %). EZ was intact in 125 eyes (66.1 %) and not intact in 64 (33.9 %). ELM was intact in 148 (78.3 %) eyes and not intact in 41 (21.7 %) eyes. Thirty-six eyes (19 %) presented not-intact EZ and ELM. RFT mean was of 132.69 ± 68.2, range 36–944 μ. MDIRS mean was of 806.8 ± 430.2, range 168–2,537 μ. (Table 2)

The comparison of the demographic and tomographic parameters between the two LMH pattern subgroups (IR split and V LMH) did not show a significant statistical difference.

Comparison of conventional ERM and atypical ERM

All cases of ILMH were associated with ERM: 117 (61.9 %) conventional ERM, 72 (38.1 %) atypical ERM. The mean of age was statistically older in atypical ERM ILMH compared to conventional ERM ILMH. The statistical analysis showed a significant prevalence of female gender, phakic condition, and PVD in the conventional ERM ILMH subgroup ($P = 0.000$). The mean BCVA was better in the conventional ERM ILMH subgroup compared to the atypical ERM ILMH subgroup ($P = 0.000$). (Table 1) The difference persisted even after excluding phakic patients for the possible influence of lens

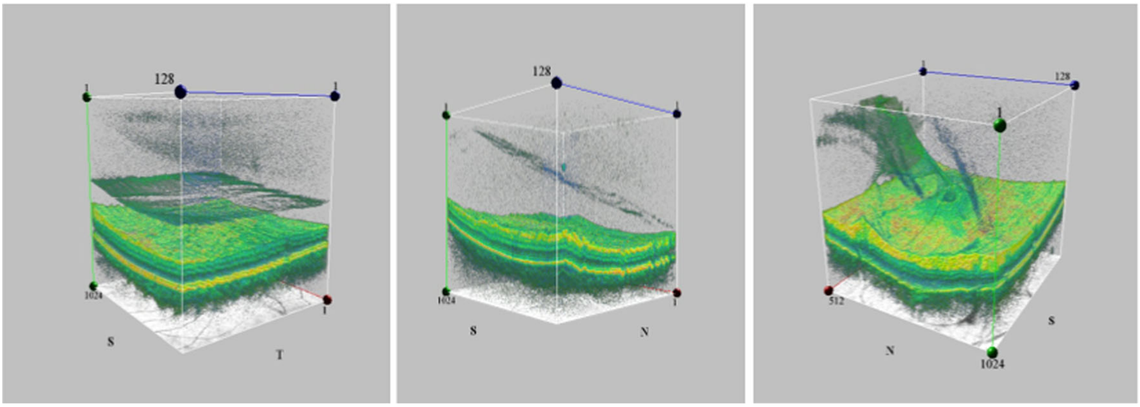

Fig. 3 Posterior vitreous detachment (PVD) analysis with three-dimensional view macular cube 512 × 128

opacities on BCVA. RFT was statistically more reduced in the atypical ERM ILMH subgroup compared to the conventional ERM ILMH subgroup ($P = 0.000$). The statistical analysis showed a significant association between the interruption of the outer retinal layers (EZ and ELM) and the atypical ERM ILMH subgroup ($P = 0.000$).

The role of the outer retinal layers

The whole group of patients was divided into four subgroups according to the integrity of EZ and ELM:

– subgroup of ILMH with intact EZ and ELM (subgroup EZi–ELMi)
– subgroup of ILMH with not intact EZ and intact ELM (subgroup EZni–ELMi)
– subgroup of ILMH with intact EZ and not intact ELM (subgroup EZi–ELMni)
– subgroup of ILMH with not intact EZ and ELM (subgroup EZni–ELMni) (Fig. 6)

The authors compared the BCVA, as dependent variable, between the two subgroups of patients that were affected by EZ damage but differed in integrity of ELM: the EZni–ELMi and EZni–ELMni subgroups. The statistical analysis showed a significant correlation between BCVA and integrity of ELM ($P = 0.000$) (Fig. 6).

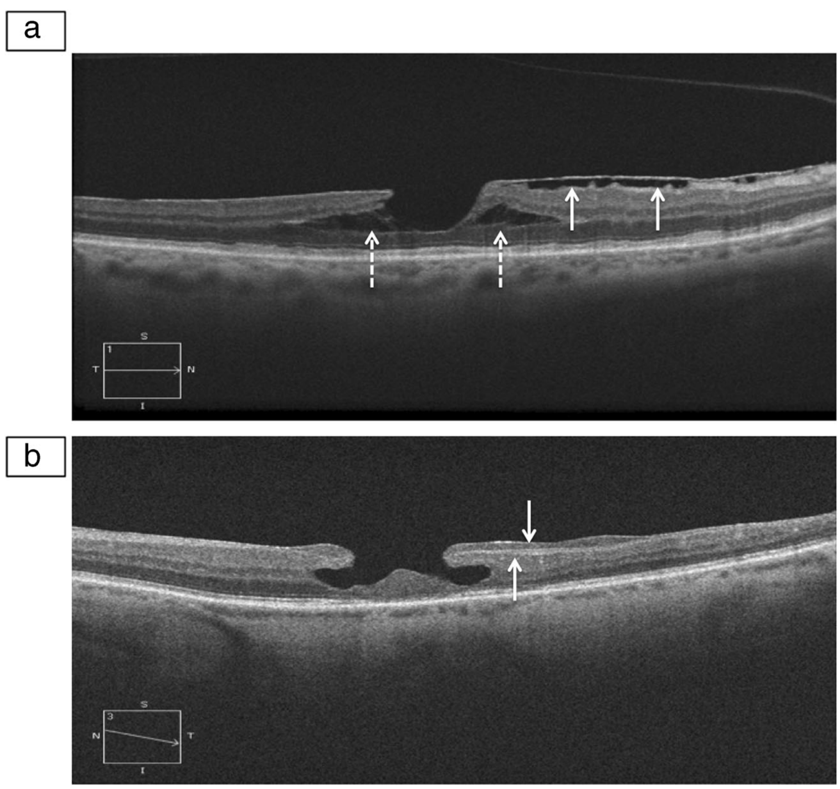

Fig. 4 **a** Conventional epiretinal membrane (ERM): *white arrows* show ERM, *white dashed arrows* show intraretinal cysts due to tractional forces. **b** Atypical ERM: *white arrows* show atypical ERM

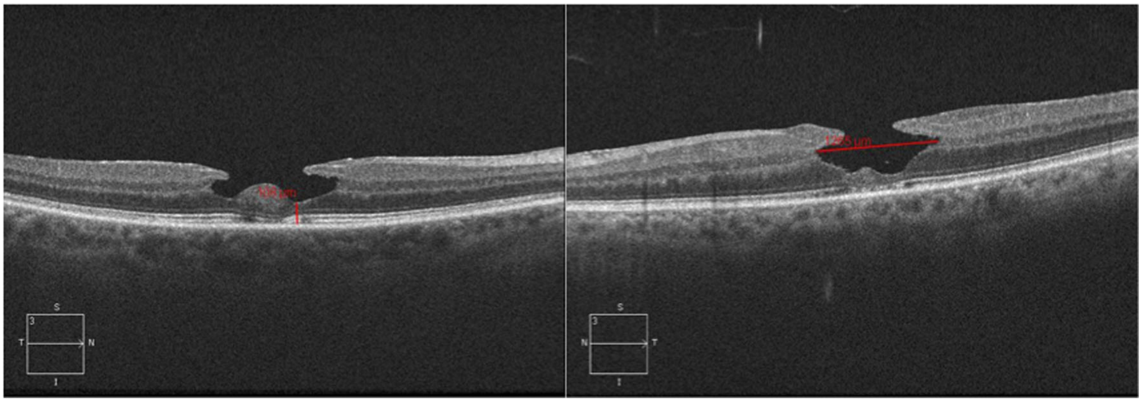

Fig. 5 Morphometric parameters. Residual foveal thickness (RFT) micron (μ). Maximal diameter of intraretinal splitting (MDIRS) (μ)

Follow-up

Data collection was completely performed for 68 eyes of 62 patients (50 females and 12 males) at 12 months, and for 35 eyes of 33 patients (24 females and 9 males) at 24 months.

The statistical analysis did not show significant changes in BCVA at different time points of follow-up in the whole group and in the subgroups of ERM type.

The authors found that RFT significantly decreased in the atypical ERM ILMH subgroup at 24 months compared to time point 0 ($P = 0.027$), a progressive increase of MDIRS in both subgroups at 12 months (conventional ERM ILMH subgroup $P = 0.000$; atypical ERM ILMH subgroup $P = 0.037$) and in the atypical ERM ILMH subgroup at 24 months ($P = 0.007$) was highlighted. (Fig. 7)

Discussion

This study confirms some findings already published by other authors, and highlights additional information not yet published. Although a specific clinical entity of ILMH associated with atypical ERM has not yet been defined, many characteristics of this membrane have been discovered. Recent studies about the composition and morphology of the two different ERMs associated with ILMH have strengthened the hypothesis that they could be two distinct entities [3, 8].

In the light of the results, atypical ERM is associated with a more severe clinical entity compared to conventional ERM. Atypical ERM is characterized by poorer visual acuity and thinner RFT than conventional ERM, confirming the data reported by recent studies [4–7].

The first new observation focuses on the shape of ILMH. The authors reviewed the diagnostic criteria of ILMH and proposed two LMH patterns: the classic one with intraretinal splitting that meets Witkin's criteria, and the other one V-shaped LMH. V-shaped LMH presented a similar tomographic morphological profile of macula pseudohole (MPH). However, MPH, firstly described by Gass, has been defined as a macular lesion that does not have a loss of retinal tissue [10]. Instead, V-shaped LMH is characterized by outer nuclear layer (ONL) defects with or without an involvement of outer

Table 1 Demographic and functional data of epiretinal membrane (ERM) type subgroups and of the whole group of patients

ERM type	*N* (%)	Age° years mean ST DV range	Sex§ female/ male (*n*)	Eye§ right/ left (*n*)	Lens§ phakic/ pseudophakic (*n*)	BCVA° LogMar (mean ST DV)
Conventional ERM	117	71.56 ± 8.81	76/27	55/62	93/24	0.14 ± 0.16
Atypical ERM	72	74.92 ± 10.63	36/36	31/41	38/34	0.39 ± 0.31
Whole-group ERM	189	72.84 ± 9.6	112/63	86/103	131/58	0.24 ± 0.25
P value		0.01*	0.00*	0.59	0.00*	0.00*

Legend

ST DEV standard deviation

° Mann–Whitney U test

§ Pearson's chi-square test

* significant

Table 2 Tomographic parameters of epiretinal membrane (ERM) type subgroups and of the whole group of patients

ERM type	*n.*	RFT° µ micron (mean ST DEV)	MDIRS° µ micron (mean ST DEV)	LMH§ IR split/V-shaped	PVD§ yes/no	EZ§ I/NI I = intact NI = not intact	ELM§ I/NI I = intact NI = not intact
Conventional ERM	117	152.15 ± 77.25	844.17 ± 483.74	89/28	103/11	114/3	109/8
Atypical ERM	72	101.06 ± 29.37	746.07 ± 319.18	52/20	26/43	11/61	39/33
Whole-group ERM	189	132. 69 ± 68.02	806.80 ± 430.28	141/48	129/54	125/64	148/41
P value		0.00*	0.44	0.55	0.00*	0.00*	0.00 *

Legend

RFT residual foveal thickness

MDIRS maximal diameter of intraretinal splitting

LMH lamellar macular hole

IR split Intraretinal splitting

PVD posterior vitreous detachment

EZ ellipsoidal zone

ELM external limiting membrane

ST DEV standard deviation

° Mann–Whitney U test

§ Pearson's chi-square test

* significant

retinal layers. (Fig. 8) The diagnosis of V-shaped LMH with intact ELM was based on the ONL thickness reduction from the perifoveal to foveal area because the Henle fiber layer (HFL) integrity and the differentiation by the ONL are not always evaluable, depending on the measurement beam position [11–13]. On the contrary, the V-shaped LMH with not-intact ELM implies the involvement of the ONL. In addition, the difference between V-shaped LMH and MPH is confirmed by the different RFT between those: the RFT mean of MPH reported in the literature is 167 microns, whereas the RFT mean of V-shaped LMH, in this study, is 128.57 microns [2].

In the current study, the difference between RFT of V-shaped ILMH with atypical ERM and RFT of V-shaped ILMH with conventional ERM was statistically significant ($P = 0.000$), confirming the greater severity of ILMH with atypical ERM compared to that with conventional ERM. It remains unknown why some types of ILMH develop an intraretinal splitting and some do not. In myopic LMH with posterior staphyloma recruited during the current study and analyzed separately, some cases of V-shaped LMH developed intraretinal splitting during the follow-up [14]. In the series of ILMH, no morphological changes were found.

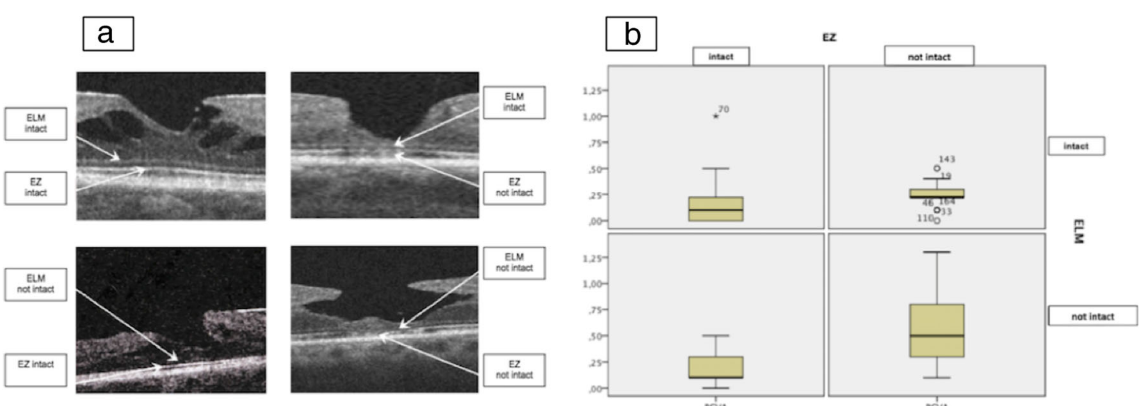

Fig. 6 **a** ILMH with or without integrity of ellipsoid zone (EZ) and external limiting membrane (ELM). **b** Boxplot of four subgroups of ILMH with and without integrity of EZ and ELM

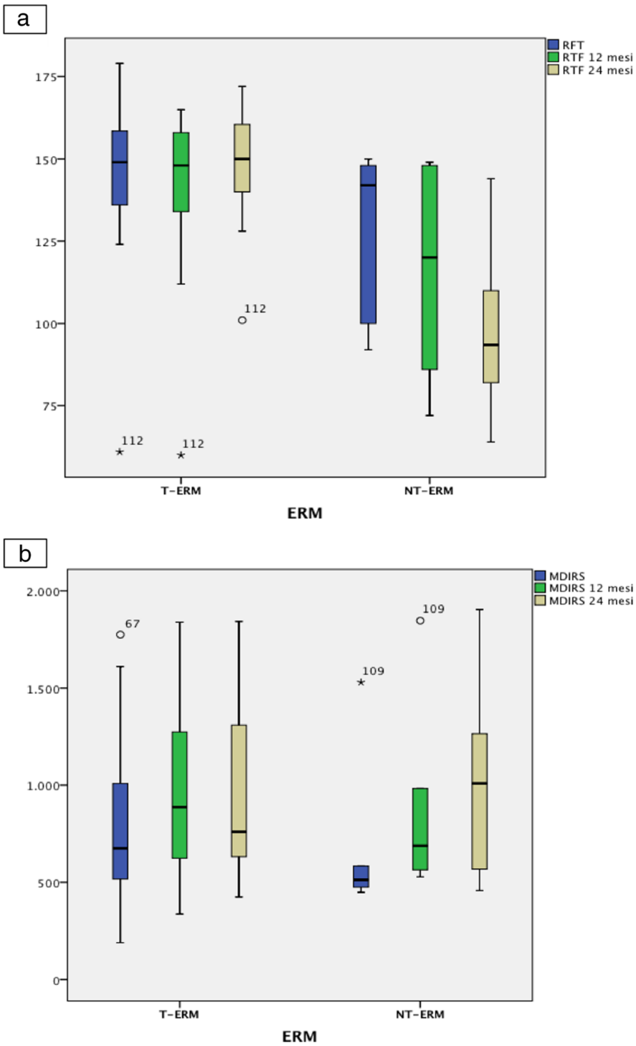

Fig. 7 **a** Boxplot of RFT mean of ILMH with conventional and atypical epiretinal membrane (ERM) at 0, 12, and 24 months of follow-up. **b** Boxplot of MDIRS mean of ILMH with conventional and atypical ERM at 0, 12, and 24 months of follow up

The second observation highlights the role of outer retinal layers in visual function. Wakabayashi and recently Schumann have demonstrated a significant correlation between ELM integrity and BCVA after surgery for MH and ILMH treatment respectively [8, 15]. In the current study, the authors first showed the association between ELM integrity and higher BCVA before surgery. BCVA mean of ILMH with not-intact EZ and intact ELM was better than BCVA mean of ILMH with not-intact EZ and ELM, highlighting the important functional role of ELM. BCVA does not only depend on the EZ but also on the ELM. In light of the recent definition of ELM as a border between the outermost aspect of the ONL, composed of photoreceptor cell bodies, and EZ, the ELM integrity could be a good preoperative indirect parameter for assessing the degree of microstructural changes in the photoreceptor cell bodies.

The third observation is about the role of the vitreous body. The pathogenesis of ILMH is not clearly established. Recent studies have reported a different composition of conventional and atypical ERM. Schumann et al. analyzed surgically excised flat-mounted internal limiting membrane specimens and ERM specimens removed from 25 eyes of 25 patients with ILMH [8]. Specifically, the cell composition of ERM using interference and phase-contrast microscopy, immunocytochemistry, and transmission electron microscopy were studied, showing that ILMH associated with epiretinal proliferation, corresponding to atypical ERM, is composed of fibroblasts and hyalocytes without contractive components, whereas conventional ERM is composed of myofibroblasts with contractive properties. Schumann et al. concluded that cells within ILMH with atypical ERM appeared to originate from the vitreous and possessed less contractive properties than cells of conventional ERM. In the current study, the vitreous body was frequently detached in ILMH with conventional ERM; in contrast, it was attached in most cases of ILMH with atypical ERM, supporting the hypothesis of the role of vitreous in the pathogenesis of atypical ERM. It is not clear why few cases of ILMH with atypical ERM were associated with PVD, as reported by the authors and by Compera [9]. Probably, part of the vitreous cortex, after detachment, could remain attached to retinal surface allowing the development of atypical ERM.

The last observation regards the evolution of ILMH. Bottoni et al. published the results of the natural evolution of ILMH, emphasising that ILMH is a stable condition during lifetime [4]. In the current study, RFT and MDIRS in both subgroups of ERM were compared. The authors noticed that there was an increase of MDIRS in both subgroups of ERM and a reduction of RFT in atypical ERM subgroup during the follow-up, but any significant change of BCVA was not demonstrated. In the light of morphological changes outlined, it could not be stated that ILMH is a stable condition with a tissue defect that does not vary over time; rather, the amount of morphological changes is so slow and gradual that it will not cause, during the time range of follow-up, significant functional changes. The increase of MDIRS is secondary to tangential traction in ILMH with conventional ERM, while the reduction of RFT and the increase of MDIRS in ILMH with atypical ERM are secondary to a pathological process that determines a slow gradual involvement of the outer retinal layers and a subsequent progressive deterioration of BCVA.

In conclusion, the current study demonstrated that ILMH was not a stable condition during the 2 years of follow-up, showing morphological changes and an involvement of the outer retinal layers. Specifically, an important role of ELM in preserving the visual acuity was established. ILMH with atypical ERM is a more severe clinical entity compared to ILMH with conventional ERM. The prevalence of vitreous

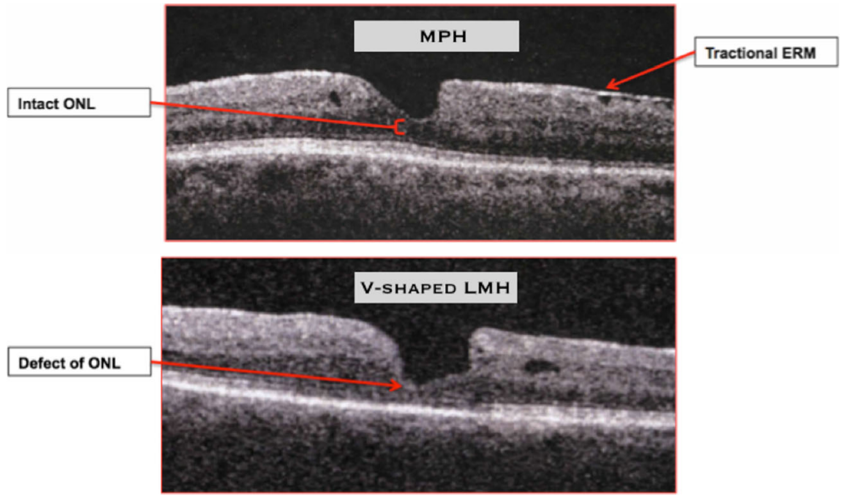

Fig. 8 Comparison of MPH and V-shaped ILMH

adhesion in ILMH with atypical ERM supports the hypothesis of the role of vitreous in the pathogenesis of atypical ERM.

Compliance with ethical standards

Funding No funding was received for this research.

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

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.

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

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