Lamellar Macular Holes Associated with End-Stage Exudative Age-Related Macular Degeneration

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ABSTRACT: **Background:** Reports of lamellar macular holes (LMHs) with underlying age-related macular degeneration (AMD) are rare, and the specific definition, pathogenesis and surgical recommendations for this macular condition remain unclear.

Objectives: To present a series of LMHs in eyes with underlying end-stage AMD, and describe optical coherence tomography (OCT) detection of associated morphologic abnormalities.

Methods: We reviewed the files of consecutive patients diagnosed with LMH and underlying end-stage AMD between September 2007 and September 2011.

Results: Sixteen eyes of 14 patients were included in this study. The average follow-up after the OCT-established diagnosis of LMH was 19.8 months (range 4–48). The average visual acuity (VA) at last follow-up visit was 20/400 (20/60–20/1200). The best-corrected VA was stable in 10 eyes (62.5%) and deteriorated in 6 (37.5%). There was a statistically significant correlation between VA and minimal foveal thickness (r = -0.598, P = 0.014).

Conclusions: In this series of LMHs with underlying AMD the OCT findings were intraretinal fluid, cystic spaces and window defect.

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KEY WORDS: age-related macular degeneration (AMD), end-stage AMD, lamellar macular hole (LMH), optical coherence tomography (OCT)

Lamellar macular holes (LMHs) are usually the result of an incomplete process of macular hole formation in which the roof of the foveal pseudo-cyst opens, while the floor of the pseudo-cyst located in the outer retina appears to remain intact [1-3]. Other causes of LMH include rupture of the inner wall of large central cysts in cystoid macular edema [4] and possible epiretinal membrane (ERM) tangential traction [5]. LMHs due to incomplete macular hole (MH) formation are usually stable over time, and visual acuity (VA) of the involved eyes is often moderately impaired [6].

Age-related macular degeneration (AMD) affects more than 1.75 million individuals in the United States alone. The overall prevalence of neovascular AMD and/or geographic atrophy in the U.S. population 40 years and older is estimated to be 1.47%. The prevalence of late AMD increases steeply with age, differing in individuals of different ethnic backgrounds [7] and affecting 11.5% of white persons older than 80 years [8]. However, reports of LMHs with underlying AMD are rare (only one case reported in the literature) [9], and the specific definition, pathogenesis and surgical recommendations for this macular condition remain unclear.

We present a retrospective observational case series of 16 eyes in 14 patients who presented with an LMH with underlying AMD that had been diagnosed by optical coherence tomography (OCT). The aim of the study is to describe the morphologic abnormalities associated with LMH with underlying end-stage AMD as revealed by OCT.

MATERIALS AND METHODS

The study and data accumulation were carried out with approval of the Meir Medical Center Institutional Review Board. The study protocol and data collection adhered to the tenets of the Declaration of Helsinki.

We searched the OCT database of our department and retrieved the files of consecutive patients diagnosed as having LMH with underlying end-stage non-exudative or exudative AMD between September 2006 and September 2011. The exudative AMD cases comprised both sub-foveal and juxtafoveal choroidal neovascularization. This series included 7 males and 7 females whose mean age was 80.6 years (range 58–90). Best-corrected visual acuity (BCVA), biomicroscopic examination, and OCT scan (either by stratus OCT Carl Zeiss Meditec, Dublin, CA, USA, or Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) were recorded in all patients. VA was measured on a Snellen chart and converted into the logarithm of the minimum angle of resolution for statistical analysis. We recorded the biomicroscopic diagnosis of the retina specialist as had been noted in the patient's file before the OCT examination was carried out.

LMHs were defined according to the definition of Haouchine et al. [2], which included central foveal thinning, normal or moderately increased perifoveal retinal thickness, and irregular

foveal floor surrounded by edges split horizontally by a cleft separating the inner and outer retina. AMD was diagnosed by biomicroscopy, fluorescein angiography and OCT. Eyes with other retinal pathology (e.g., high myopia, vein occlusion, diabetic retinopathy) or uveitis were excluded from the study.

Macular imaging with the OCT stratus included six radial scans each 6 mm long for each eye, using the macular thickness protocol. The scans were centered on the fixation point, with adjustments made by the examiner to ensure that the scan passed through the center of the hole. Imaging with the Spectralis OCT was carried out according to the "posterior pole" protocol: scan size 30 x 25 degrees, angular orientation 7 degrees, 61 section scans, and a 120 micron (μ) distance between sections. The scans were considered to be of adequate quality if the OCT software correctly identified the inner and outer boundaries of the retina. All calculations were performed manually using the software calipers. The retina was measured at the thinnest point at the base of the lamellar hole [2]. All scans were examined to identify the one scan that crossed the thinnest part of the base. The diameter of the LMH was also calculated manually by means of calipers placed on the edge of the hole and all scans were examined in order to find the largest diameter hole.

Retinal thickness was also measured at a point 750 μ from the center of the macula nasally and temporally on the horizontal line. The nasal and temporal thickness measurements were averaged; the result represents the perifoveal thickness measurement according to Haouchine et al. [2]. The evaluation at every follow-up visit included BCVA (Snellen), slit-lamp biomicroscopy, and a repeat OCT exam. The main outcome measures were BCVA, the maximal diameter of the LMH opening (the base diameter of the defect), the diameter of inner orifice (opening diameter), minimal foveal thickness, and perifoveal thickness. Also recorded were the OCT findings of an ERM, intraretinal fluid cystic spaces, subretinal fluid (SRF), pigment epithelial detachment (PED), and a window defect that strongly depicted the choroid, indicating retinal pigment epithelium (RPE) and photoreceptor loss.

STATISTICAL ANALYSIS

All data collected in the study were inserted into an electronic database via Microsoft Excel 2007 (Microsoft Corporation, Redmond, Washington, USA). Statistical analyses were performed using SPSS 21.0 (SPSS, Inc, Chicago, IL). Results are expressed as mean ± SD, mean (range) or N (%). Pearson correlation was used to analyze the relationship between VA and minimal foveal thickness.

RESULTS

The 14 patients (16 eyes) who met the study entry criteria had an average age of 80.6 years (range 58–90 years) and included 7 males and 7 females. All identified cases of LMH were end-stage wet (exudative) AMD. Before LMH formation, one eye had 2 laser treatments for juxtafoveal choroidal neovascularization, one eye had 2 photodynamic treatments, each of two eyes had an intravitreal injection of triamcinolone acetonide, one eye had 2 intravitreal injections of ranibizumab, and 12 eyes had 3 to 16 intravitreal injections of bevacizumab. Mean follow-up after the OCT-established diagnosis of LMH was 19.8 months (range 4–48 months).

The mean VA at presentation was 20/114 (range 20/30–20/800) and it deteriorated to 20/214 (20/30–20/800) after the transformation to LMH occurred. The mean VA at the end of the follow-up was 20/400 (range 20/60–20/1200) [Table 1]. After the transformation to LMH, the VA was stable in 10 eyes (62.5%) and deteriorated by more than 1 Snellen line in 6 eyes (37.5%). After dilated funduscopic examination, the retina specialist recorded having detected a macular scar in 14 eyes (87.5%) and severe RPE changes or atrophy in 2 eyes (12.5%). All eyes demonstrated clinical posterior vitreous detachment with apparent Weiss rings.

OCT imaging demonstrated a highly reflective, but thin line on the surface of juxtafoveal retina, which appeared to be an ERM, a taut internal limiting membrane (ILM), or a posterior hyaloid membrane in all of the studied eyes [Figures 1 and 2, Table 2]. All the eyes in our series had OCT findings of intraretinal fluid cystic spaces and a window defect that depicted the choroid in greater detail, indicating RPE and photoreceptor loss [Figures 1 and 2, Table 2]. PED was observed in 6 eyes

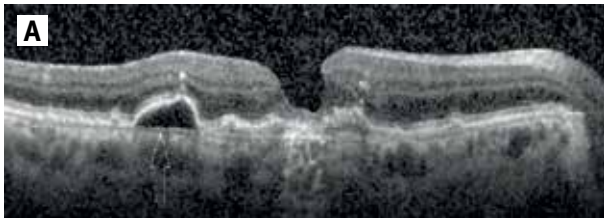
Table 1. Patient characteristics

Patient	Eye	VA logMAR		
		Before LMH formation	After LMH formation	Last follow-up
1	Right	1.6	1.6	1.6
2	Right	0.4	0.52	0.7
3	Right	1	1.6	1.6
4	Left	1.5	1.4	1.5
5	Left	0.52	0.95	1.3
6	Right	0.52	0.52	0.52
7	Left	0.4	1	1
8	Right	0.4	0.52	0.7
8	Left	0.52	1.3	1.8
9	Left	1.8	1.6	1.6
10	Right	0.3	1.3	1.6
11	Right	1.3	1.50	1.5
12	Left	0.7	1.00	1.3
13	Right	0.52	0.52	1.6
13	Left	0.22	0.22	0.7
14	Right	0.4	1.00	1.6

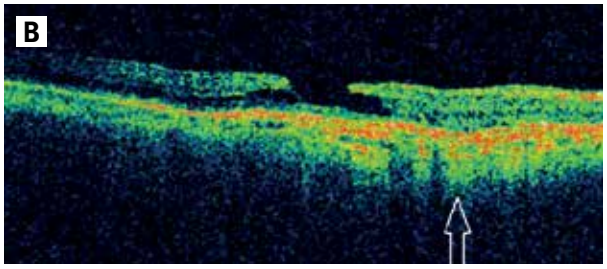
LMH = lamellar macular hole, VA = visual acuity

Figure 1. Optical coherence tomography scan of a lamellar macular hole with underlying age-related macular degeneration. The arrows indicate:

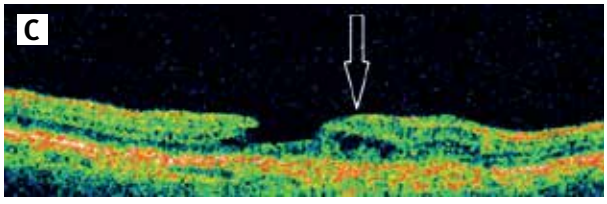
[A] A pigment epithelial detachment



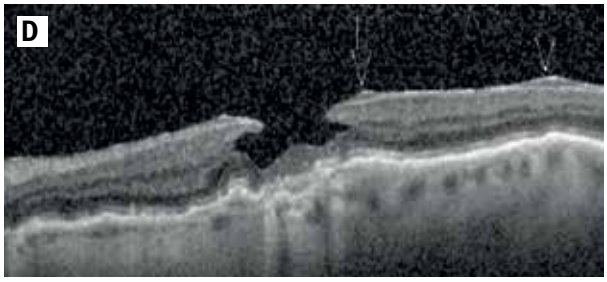
[B] A window defect depicting the choroid in greater detail, indicating RPE and photoreceptor loss



[C] Intraretinal fluid cystic spaces



[D] An epiretinal membrane



[E] Subretinal fluid

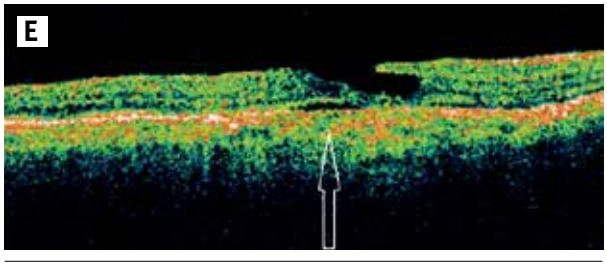
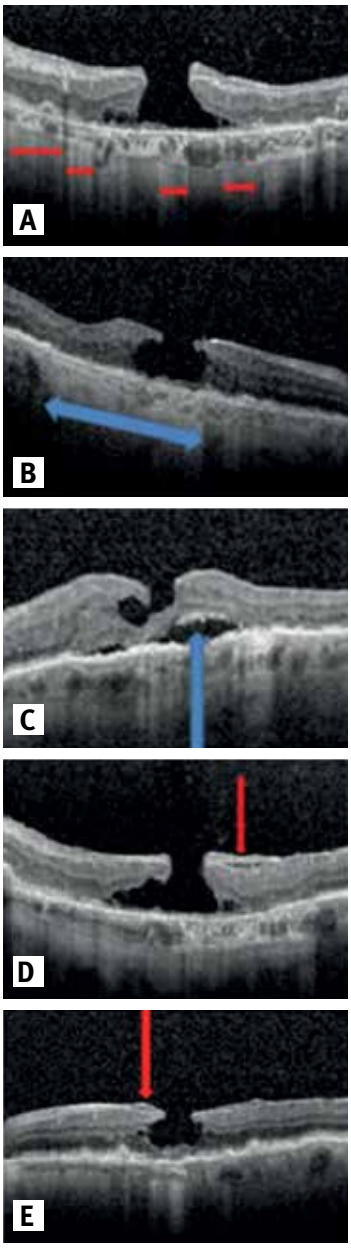


Figure 2.
Optical coherence tomography scan of a lamellar macular hole with underlying age-related macular degeneration. The markers indicate:

[A and B] A window defect depicting the choroid in greater detail, indicating RPE and photoreceptor loss

[C] Subretinal fluid

[D and E] An epiretinal membrane



(37.5%) and SRF was detected in 2 eyes (12.5%) [Figures 1 and 2, Table 2].

The average maximal LMH diameter was 1071 (± 411) μ, and the average inner opening diameter 478.3 (± 132) μ. The average minimal foveal thickness was 39.8 (± 28.5) μ, and the average perifoveal thickness 299.5 (± 45.1) μ. The VA correlated significantly with the minimal foveal thickness (r = -0.598, P = 0.014), i.e., the deeper the lamellar defect, the poorer the VA.

Table 2. Optical coherence tomography findings

Eye	Maximal hole width (μ)	Inner opening diameter (μ)	Minimal foveal thickness (μ)	Perifoveal thickness (μ)	Intraretinal fluid cystic spaces	ERM	Window defect	PED	SRF
1	1402	461	29	427	+	+	+	+	
2	860	611	85	307	+	+	+		
3	1535	511	15	255	+	+	+		
4	2200	661	17	335	+	+	+	+	+
5	1260	570	72	308	+	+	+		
6	1110	486	70	287	+	+	+		
7	910	511	32	251	+	+	+		
8	736	586	25	292	+	+	+	+	
9	1085	412	17	265	+	+	+		+
10	649	235	27	271	+	+	+	+	
11	835	699	15	264	+	+	+	+	
12	781	402	20	303	+	+	+		
13	750	512	21	252	+	+	+		
14	1003	374	78	338	+	+	+		
15	723	336	93	335	+	+	+		
16	1297	286	21	302	+	+	+	+	

ERM = epiretinal membrane, PED = pigment epithelial detachment, SRF = subretinal fluid, (+) = present, ( ) = absent

DISCUSSION

OCT is capable of revealing morphologic abnormalities associated with LMHs in eyes with underlying end-stage AMD. After careful analysis of the literature, we could not find a similar study. Our Medline search yielded a single case report in the literature, where Theodossiadis et al. [9] describe a patient who had LMH with exudative AMD. OCT demonstrated an ERM-associated LMH with coexisting subretinal fluid. The patient was treated with vitrectomy, ILM peeling and gas. The results of that treatment were complete closure of the LMH with total SRF absorption and VA improvement.

LMH usually results from an abortive process of macular hole formation related to perifoveal posterior hyaloid detachment [1-3]. In most cases, idiopathic LMH is a stable condition with moderately good VA. At presentation, Haouchine and co-authors [2] reported a mean VA of 20/40 (range 20/20–20/200), Witkin et al. [10] reported a mean VA of 20/40 (range 20/20–finger count 2.5 m), Garretson and team [11] reported a mean VA 20/80 (range, 20/40–20/120), and Ophir et al. [12] reported a mean VA of 20/66 (range 20/30–20/240). The mean VA in our study was 20/400 (range 20/60–20/1200), and we believe the possible cause of this poor VA was the underlying AMD which is associated with poorer VA due to photoreceptor loss and/or RPE atrophy and/or retinal damage.

We found a significant correlation between VA and minimal foveal thickness (r = -0.583, P = 0.022), indicating that a deeper lamellar defect is associated with a poorer VA. This is probably because the thinner the retinal floor, the more retinal damage and less likelihood of a physiologically potent retina. Our average perifoveal thickness measurements (299.5 μ) were similar to those of earlier studies on idiopathic LMH (range 278.9–338 μ) [2,10,13]. A highly reflective, but thin line on the surface of the juxtafoveal retina, which appeared to be an ERM, a taut ILM or a posterior hyaloid membrane was observed on OCT imaging in all 16 eyes included in this report. This rate is consistent with the rates of 50–100% reported in studies of idiopathic LMH [2,10,12-14]. The high percentage of eyes with ERMs suggests that ERM contraction may play a role in LMH formation, probably related to foveal destabilization and disruption of cell-to-cell adhesion caused by the underlying AMD, thereby rendering the fovea susceptible to centrifugal separation by ERM tangential traction. This is supported by the clinical finding of Weiss rings in all these patients.

All eyes in the current study displayed foveal or juxtafoveal discontinuation of the photoreceptor and/or RPE layers on OCT. The discontinuation of those hyper-reflective layers allows better penetration of the OCT laser beam, thus creating a window defect that strongly depicted the choroid. Those findings are part of the pathology of the underlying AMD disease. This observation led us to consider that the mechanism of transformation to LMH could be apoptosis and cell death following RPE and loss of the outer retina [15]. All 16 eyes in our series had OCT findings of intraretinal cystic spaces, and 2 eyes (12.5%) had SRF as well. The presence of intraretinal fluid and/or SRF in eyes with LMHs with AMD may indicate that the underlying disease was still active, suggesting an ongoing pathologic process that might be amenable to treatment. For example, anti-vascular

endothelial growth factor injections may be administered as long as there are signs of exudation on OCT, with the aim of preventing further vision loss and scotoma enlargement. Several recent studies on the treatment of idiopathic lamellar holes with vitrectomy, ERM peeling, or ILM peeling with or without gas tamponade showed good results [16,17]. Those results taken together with the case report of Theodossiadis et al. [9] cited above raises the speculation that certain cases of LMH with underlying AMD might benefit from surgery.

All the lamellar holes detected on OCT in our studied eyes were misdiagnosed on initial funduscopic examinations. This supports the value of OCT imaging as an essential tool in the diagnosis of lamellar holes with underlying AMD and adds another diagnosis to the list of pathologies best reached by OCT.

Despite the retrospective nature of this study, a unique presentation of morphologic abnormalities in a series of eyes with underlying AMD that have lamellar macular holes is described. In conclusion, OCT can reveal morphologic abnormalities associated with end-stage AMD. All the currently studied eyes demonstrated intraretinal cystic spaces, RPE or photoreceptor layer discontinuation, and ERM on OCT. There was a significant correlation between VA and minimal foveal thickness. LMH with underlying AMD can be accurately diagnosed by OCT.

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