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Spontaneous Conversion of Lamellar Macular Holes to Full-Thickness Macular Holes: Clinical Features and Surgical Outcomes

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Purpose: To describe the clinical features and surgical outcomes of patients experiencing a spontaneous conversion of a lamellar macular hole (LMH) to a full-thickness macular hole (FTMH).

Design: Retrospective, multicenter, observational case series.

Participants: Patients with LMH who experienced a spontaneous conversion to FTMH and underwent FTMH surgery.

Methods: Clinical charts and OCT features of 20 eyes of 20 patients were reviewed.

Main Outcome Measures: OCT features and surgical outcomes of FTMH derived from LMH.

Results: The mean baseline visual acuity (VA) was 0.21 ± 0.19 logarithm of the minimum angle of resolution (logMAR) (20/32 Snellen equivalent [SE]). Epiretinal proliferation was noted in 18 eyes (90%), and 14 eyes (75%) had an epiretinal membrane. At the diagnosis of FTMH, the mean VA decreased to 0.61 ± 0.50 logMAR (20/81 SE) ($P = 0.001$). The mean FTMH diameter was 224.4 ± 194.8 μm, with 15 (75%) small (≤250 μm), 2 (10%) medium (>250−≤400 μm), and 3 (15%) large (>400 μm) FTMHs. Eighteen (90%) FTMHs were sealed after 1 surgery, and 2 (10%) required an additional procedure. At the last follow-up, the mean VA was increased to 0.29 ± 0.23 logMAR (20/38 SE) ($P = 0.003$), but did not significantly differ from the baseline VA ($P = 0.071$).

Conclusions: Patients with LMH may develop an FTMH with no evidence of vitreomacular traction. A tangential traction from an epiretinal membrane may contribute to its genesis, but a progressive loss of retinal tissue and an inherent weakness of the foveal architecture in LMH eyes could be sufficient. Most FTMHs derived from LMH had a small diameter, showed epiretinal proliferation, showed limited retinal hydration, and were associated with relatively poor surgical outcomes compared with idiopathic FTMH. *Ophthalmology Retina 2021;■:1−8 © 2021 by the American Academy of Ophthalmology*

Lamellar macular hole (LMH) is a retinal condition characterized by an irregular foveal contour with a partial-thickness foveal defect. Its diagnostic criteria have recently been clarified, differentiating LMH from macular pseudoholes and epiretinal membrane foveoschisis.[1] The natural history of LMH includes a slow and progressive loss of retinal tissue, and the development of epiretinal proliferation.[2] The visual acuity (VA) of patients with LMH is generally stable over time, and therefore clinical observation is usually recommended.[3,4] However, some patients may experience anatomic changes, including a disruption of the outer retinal layers and a subsequent progressive decrease in VA. For these patients, a few studies have recently assessed the benefit of a surgical intervention, which still remains controversial with a concern related to the risk of developing postoperative full-thickness macular hole (FTMH).[5-7]

Eyes with LMH may also experience a spontaneous conversion to FTMH. A few articles have studied LMH and reported a single case or a few cases of LMH progressing to FTMH,[3,8-14] but this evolution has not been studied in a case series. Although the pathogenesis of LMH formation is still debated, one hypothesis is that LMH occurs after macular detachment of the posterior vitreous and therefore could be considered as an aborted FTMH.[1,15] Although anteroposterior or oblique vitreofoveal separation forces represent the main mechanism leading to the formation of idiopathic FTMH,[16] other pathways may be involved when FTMH occurs after a history of LMH.

The aim of this retrospective study was to assess the clinical features of eyes experiencing a spontaneous conversion of LMH to FTMH, to discuss the possible underlying mechanisms, and to evaluate their surgical outcomes.

Methods

In this retrospective case series, the medical records and spectral-domain OCT scans of patients who underwent pars plana vitrectomy for FTMH derived from LMH were reviewed. This study

https://doi.org/10.1016/j.oret.2020.12.023
ISSN 2468-6530/21

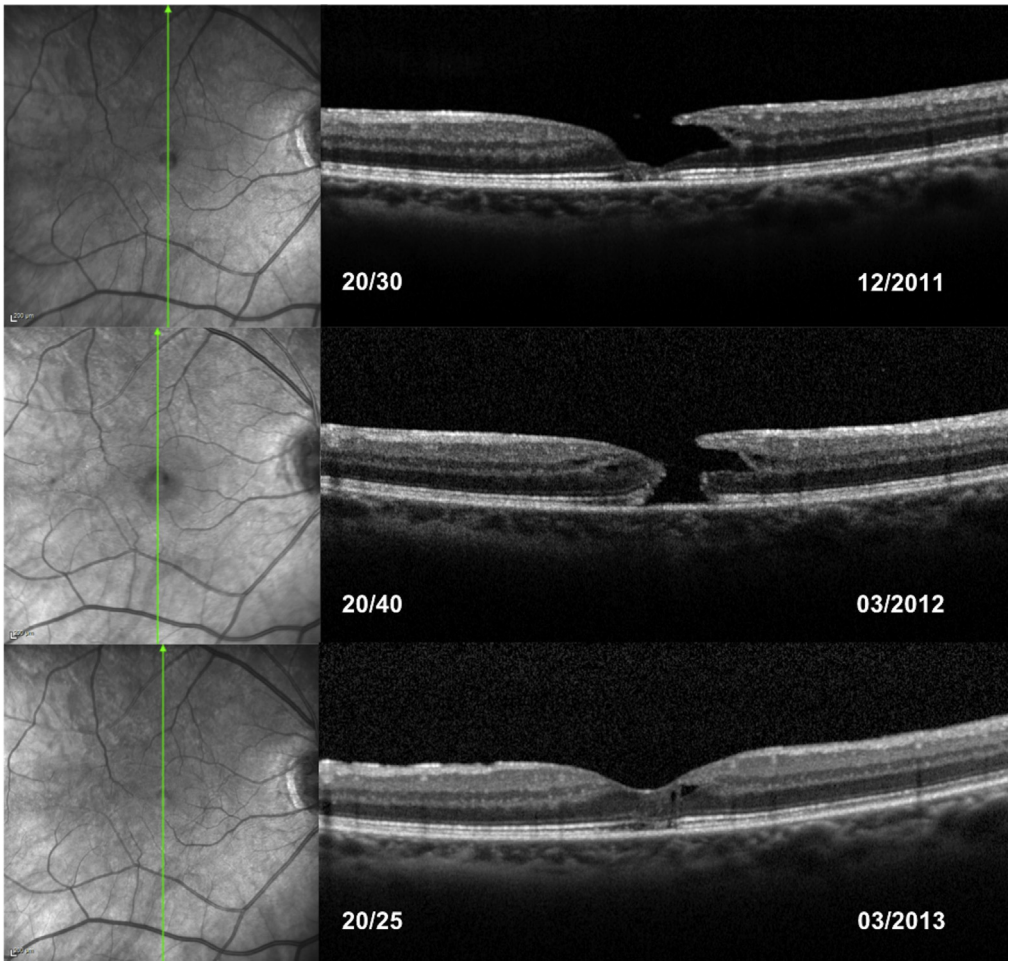

Figure 1. Sequential OCT scans showing a case of lamellar macular hole (LMH) that developed spontaneously into a full-thickness macular hole (FTMH). **Top:** The baseline OCT scan showed an LMH with outer retinal layer disruption and without epiretinal membrane. **Middle:** Three months later, the patient presented with a small FTMH with flat edges. **Bottom:** One year after surgery, persistent intraretinal cavitation and disruption of outer retinal layers were visible.

adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the French Society of Ophthalmology. All participants provided informed consent. Patients were examined in multiple international tertiary care centers between May 2011 and October 2019. The co-authors followed their respective Institutional Review Board requirements and provided de-identified clinical data and OCT imaging.

All included patients were diagnosed with LMH at baseline, experienced a spontaneous conversion to FTMH during the follow-up period, and underwent FTMH surgery (Fig 1). Patients were independently selected by the different co-authors on the basis of their own data collection. The criteria used for the diagnosis of LMH were the presence of an irregular foveal contour, the presence of a foveal cavity with undermined edges, an apparent loss of retinal tissue, and

Table 1. Patients' Characteristics

Characteristics No. Patients/Eyes	Values n = 20
Age (yrs)	68.00 ± 9.28
Gender	
Female	12 (60%)
Male	8 (40%)
Time between the diagnosis of LMH and the diagnosis of FTMH (mos)	8.30 ± 13.9
Postoperative follow-up duration (mos)	12.26 ± 19.32

FTMH = full-thickness macular hole; LMH = lamellar macular hole.

the possible presence of epiretinal proliferation.[1,17] Exclusion criteria were the presence of macular pseudohole, epiretinal membrane foveoschisis,[1] exudative age-related macular degeneration, proliferative diabetic retinopathy, and macular edema regardless of its cause. The ophthalmologic examination included at least the best-corrected distance VA measurement, slit-lamp biomicroscopy, dilated fundus examination, and spectral-domain OCT imaging using the Spectralis OCT device (Spectralis, HRA) or the Cirrus HD-OCT device (Carl Zeiss Meditec). OCT features were reassessed for the purposes of the study and included the presence of epiretinal membrane, epiretinal proliferation, and outer retinal layer (i.e., external limiting membrane, ellipsoid zone, and interdigitation zone) disruption. The term "epiretinal proliferation" was defined on OCT as a thick homogeneous layer of iso-reflective and noncontractile epiretinal material, whereas the term "epiretinal membrane" corresponded to a thin hyperreflective line over the internal limiting membrane, with tractional properties.[1] Anatomic features were assessed on at least 1 OCT B-scan, and tangential tractions on the retinal surface were defined by the presence of inner retinal folds and an increased retinal thickness on the OCT B-scan. Full-thickness macular holes were classified according to their aperture size as small ($\leq$250 μm), medium (>250−$\leq$400 μm), or large (>400 μm).[15]

All patients underwent pars plana vitrectomy for surgical repair of the FTMH. Surgical details were collected, including whether the internal limiting membrane was peeled or not and the type of tamponade agent used. Snellen VA was converted into logarithm of the minimum angle of resolution (logMAR) values for statistical purposes. The baseline VA (at the time of the diagnosis of LMH) was compared with the VA after conversion to FTMH and with the VA at the last postoperative examination.

Quantitative values are presented as a mean ± standard deviation, and qualitative values are shown as a ratio and percentage. The Wilcoxon signed-ranked test was used to compare quantitative

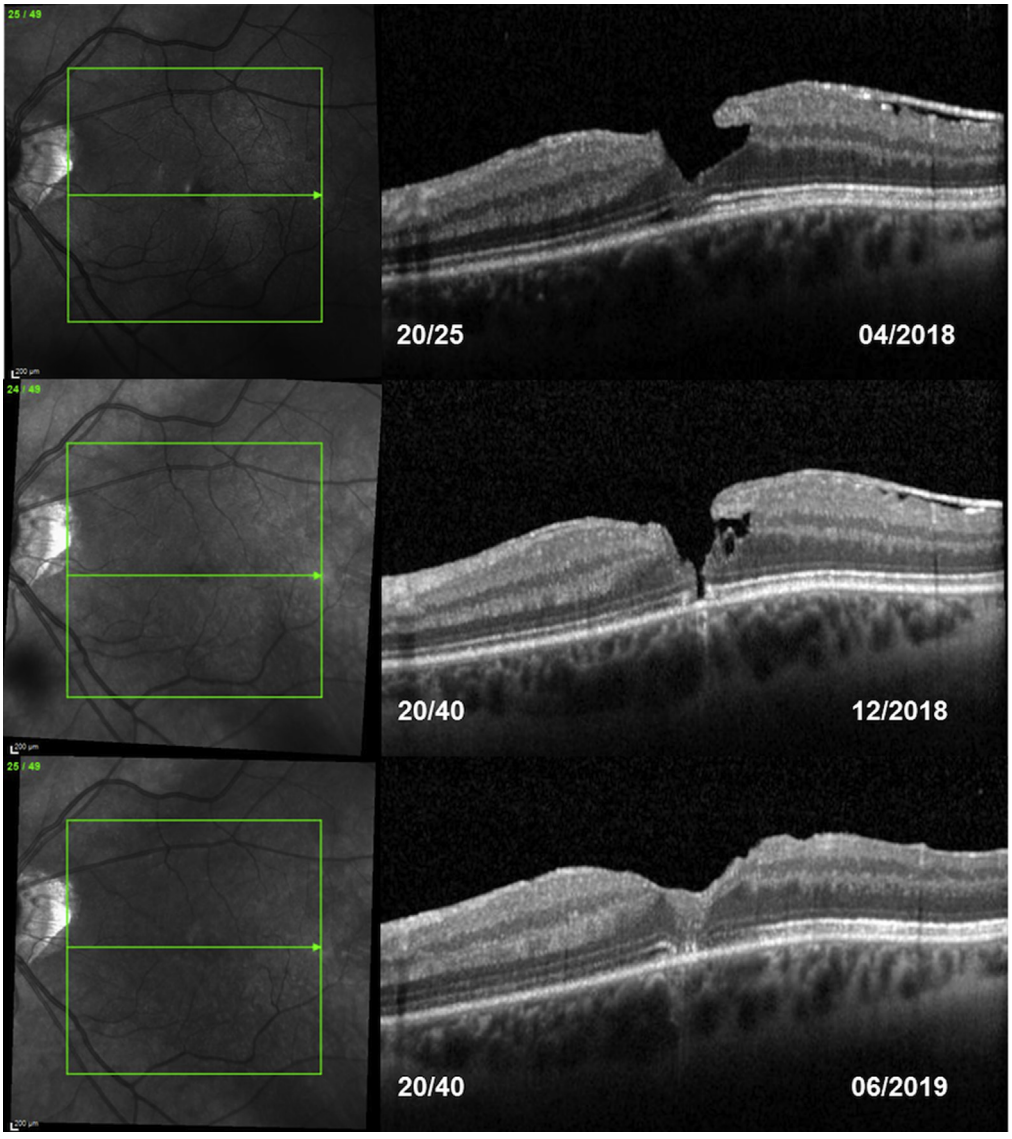

Figure 2. Sequential OCT scans of a patient with LMH who developed an FTMH and underwent pars plana vitrectomy. **Top:** At baseline, the OCT scan showed an LMH with an epiretinal membrane on the temporal part of the macula and a disruption of the outer retinal layers. **Middle:** Eight months later, a small macular hole was diagnosed. **Bottom:** After surgery, the macular hole was sealed, but the outer retinal layers were still disrupted.

variables, and the Fisher exact test was used for categorical variables. A P value less than 0.05 was considered statistically significant. All analyses were performed using XLSTAT software (Assinsoft).

Results

Twenty eyes of 20 patients (12 women and 8 men) were included. Patients' mean age at baseline was 68.5 ± 9.0 years. The characteristics of the study population are presented in Table 1.

At the time of the diagnosis of LMH, 18 eyes (90.0%) had epiretinal proliferation and 14 eyes (70.0%) had an epiretinal membrane (Fig 2). A conversion to FTMH was noted after a mean follow-up duration of 8.3 ± 13.6 months (range, 1.1−65.3 months) (Fig 1). Four of the 20 patients (20.0%) underwent cataract surgery after the diagnosis of LMH and 13.9 ± 15.1 months (range, 2.5−35.0 months) before the diagnosis of FTMH. A total of 15 of the 20 patients (75.0%) noted subjective functional changes when the FTMH occurred, and 5 patients (25.0%) had no symptoms. The mean VA decreased from 0.21 ± 0.19 to 0.61 ± 0.50 logMAR (20/32 to 20/81 Snellen equivalent [SE]; $P = 0.001$) (Fig 3).

The mean aperture size of the FTMH was 224.4 ± 194.8 μm (range, 42−839 μm). Fifteen eyes (75%) had a small (≤250 μm) macular hole, 2 eyes (10%) had a medium (between >250 and ≤400 μm) macular hole, and 3 eyes (15%) had a large (>400 μm) macular hole (Table 2). Seven eyes (35%) had elevated macular hole edges, and 13 eyes (65%) had flat macular hole edges with no or limited intraretinal cysts (Fig 4).

All eyes underwent 25-gauge pars plana vitrectomy, 18 eyes (90.0%) underwent internal limiting membrane peeling, and 18 eyes (90.0%) underwent epiretinal proliferation peeling. All eyes had gas tamponade with sulfur hexafluoride (SF_6) (17 cases), perfluoroethane (C_2F_6) (1 case), or perfluoropropane (C_3F_8) gas (2 cases). The internal limiting membrane peeling was assisted by dye staining, including triamcinolone acetonide, brilliant blue, or indocyanine green. The presence of an epiretinal proliferation precluded adequate internal limiting membrane or epiretinal membrane staining (Fig 5) and made peeling more difficult than usual. The difficulty could be overcome by peeling the epiretinal proliferation before staining the internal limiting membrane again or by starting the internal limiting membrane dissection beyond the limits of the epiretinal proliferation.

In 18 eyes (90.0%), macular holes were closed after primary vitrectomy. In 2 other eyes, although it was small, the FTMH did not close after ILM peeling and SF_6 gas tamponade. The second procedure required the enlargement of the internal limiting membrane peeling and C_3F_8 gas tamponade to achieve MH closure. After a mean follow-up of 12.3 ± 19.3 months (range, 0.23−88.03 months) after FTMH surgery, the VA increased to 0.29 ± 0.23 logMAR (20/38 SE) and was significantly improved compared with the preoperative VA ($P = 0.003$), but was not significantly different from the baseline VA ($P = 0.071$) (Fig 4). No significant differences were found in the rate of outer retinal layers disruption between baseline (at the time of the diagnosis of LMH) and the last follow-up examination (Table 3).

Discussion

An LMH is known to be relatively stable over time.[2,3] However, this study showed that LMH could occasionally evolve spontaneously to FTMH, for which a surgical intervention was required.

Although the formation of idiopathic FTMH is most often due to a posterior hyaloid traction on the fovea during the process of perifoveal detachment of the vitreous,[16,18] other pathways could be involved when an FTMH occurs within a preexisting LMH. In 2001, Haouchine et al[19] showed that a vitreoretinal traction could disrupt the inner third of the foveola with a cyst formation visible at the OCT examination. This could be the first step of FTMH formation, but may also result in LMH development when

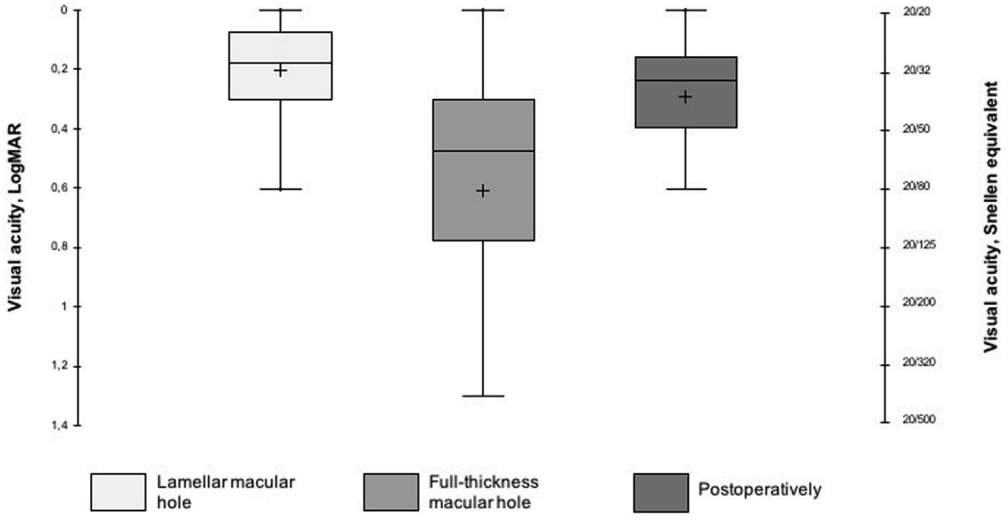

Figure 3. Visual acuity (VA) changes throughout the follow-up. The mean VA decreased significantly from 0.21 ± 0.19 logarithm of the minimum angle of resolution (logMAR) (20/32 Snellen equivalent [SE]) at baseline to 0.61 ± 0.50 logMAR (20/81 SE) after conversion to an FTMH ($P = 0.001$). Postoperatively, the mean VA reached 0.29 ± 0.23 logMAR (20/38 SE) at the last follow-up examination and was significantly improved compared with the VA measured before FTMH surgery ($P = 0.003$), but remained slightly lower than the baseline VA, with no significant difference ($P = 0.071$).

Table 2. FTMH Characteristics

Characteristics No. of FTMH	Values n=20
Size	
Small (≤250 μm)	15 (75%)
Medium (>250–≤400 μm)	2 (10%)
Large (>400 μm)	3 (15%)
Aperture diameter (μm)	
Mean	224
Median	164
Range	(42–839)

FTMH = full-thickness macular hole.

the roof of the pseudocysts opens with no disruption of the outer retinal layers.[16,19] Thus, one hypothesis is that a posterior vitreous detachment is the *primum movens* of LMH formation, although other mechanisms could be involved.[2,19]

The cause of the evolution of an LMH to an FTMH remains hypothetical. One mechanism could involve a tangential traction from an epiretinal membrane, as seen in 70% of our cases at baseline.[20] However, no epiretinal membrane was present at baseline in 30% of cases, so other hypotheses should be considered.

In 1969, Yamada[21] described the ultrastructure of the fovea and noted the presence of a relatively large amount of Müller cells in the foveal center. In 1999, Gass[18] commented on Yamada's findings and coined the expression "Müller cell cone" to name the structure of the foveolar center with an outer apex of approximately 40 μm in front of the "bouquet de cones centraux" and an inner base of 200 μm at the inner limiting membrane. The exact nature of the Müller cell cone has been elucidated by Bringman et al.[22-25] The central stalk of Müller cells runs vertically from the outer to the inner limiting membrane and, unlike Müller cells from the foveal wall, has no contact with the axons of the cones except near its apex.[23] Besides central Müller cells, Müller cells from the foveal wall and the parafovea have a characteristic "z-shape" with their outer processes running horizontally together with cone axons through the Henle fiber layer.[23] Under normal conditions, the structural stability of the fovea is provided by both Müller cell populations, that is, the cells of the Müller cell cone and Müller cells from the foveal wall.[24] The inner expenses of the Müller cell cone ensure the coherence of the foveal floor. However, the absence of cellular connections between the Müller cell cone and the Müller cells from the foveal wall could explain that an avulsion of the Müller cell cone results in a dissociation between the inner and outer retina in the foveal edge as previously hypothesized.[19]

In LMH, the outer nuclear layer is more or less damaged and thinned, while the external limiting membrane is initially preserved.[1,2] It is likely that, in some cases, a slow degenerative process occurs in the remnants of the outer nuclear layer, weakened by the loss of central Müller cells. This could explain both the progressive enlargement of the LMH cavitation[1,2,25] and ultimately the breakdown of the external limiting membrane and progression to FTMH.[2,25] Most of our cases showed a significant thinning of the foveal floor and a fragmentation of the ellipsoid zone or the external limiting membrane. However, no control group with an LMH that did not progress to FTMH was studied here to ascertain that these particularities increased the risk of LMH progression to FMTH. Further larger and consecutive series are needed to define more precisely cases at risk of FTMH conversion. When monitored, patients with a diagnosis of LMH should be advised to consult earlier in case of sudden VA loss.

In our series, FTMH derived from LMH showed peculiar clinical features, including a small aperture diameter in 75%

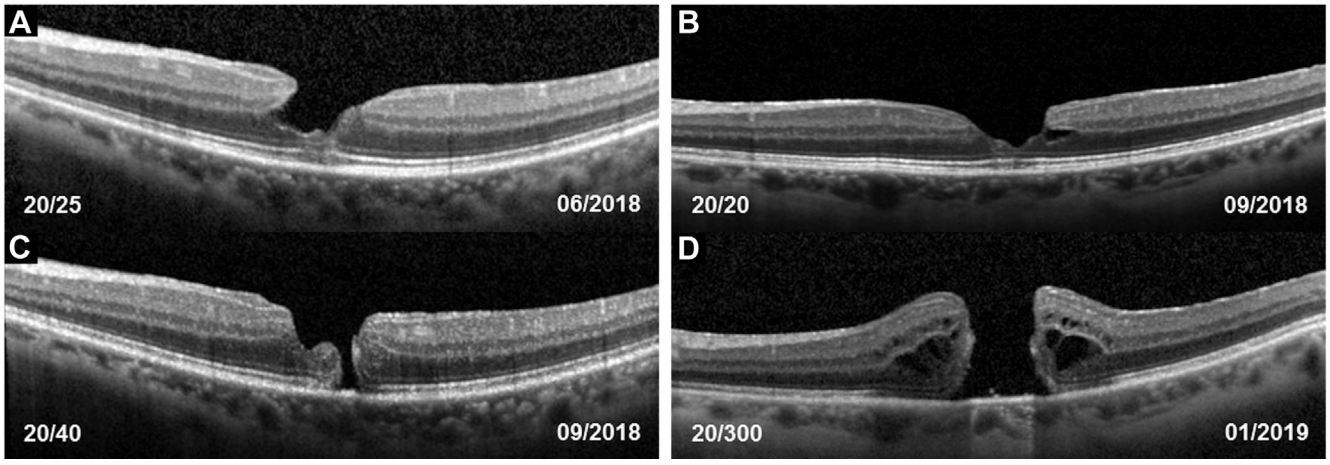

Figure 4. OCT scans of 2 patients with LMH who developed an FTMH. **A,** The first patient had an LMH with epiretinal proliferation over the retinal surface. **B,** He developed a small FTMH with flat edges and no intraretinal cysts. **C,** The second patient had an LMH with epiretinal proliferation. **D,** He developed a large FTMH with elevated edges and intraretinal cysts within the inner and outer retinal layers.

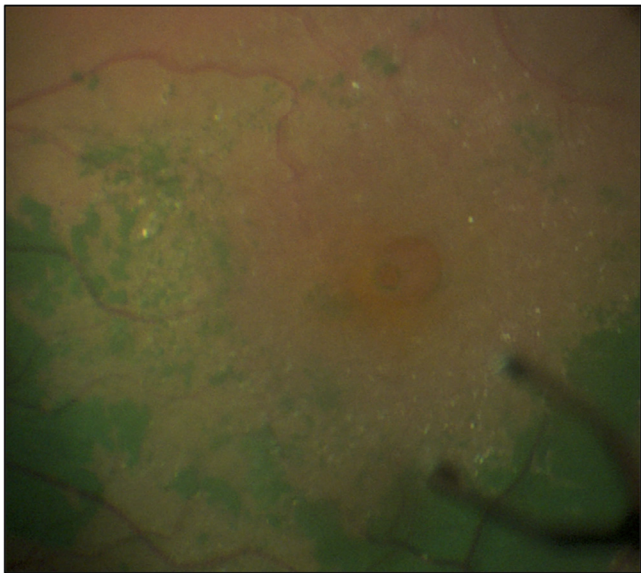

Figure 5. Intraoperative picture of a case of FTMH derived from an LMH. Indocyanine green dye was used, but the epiretinal proliferation that covered the internal limiting membrane around the hole did not stain compared with the internal limiting membrane in the peripheral part of the macular area.

of cases, a high rate (90%) of epiretinal proliferation (also called "lamellar hole-associated epiretinal proliferation"),[17] and flat edges with limited retinal hydration. The postoperative closure rate (90%) was not as good as expected, with 2 small macular holes that required a second operation to be closed.[26,27] Surgery allowed improving the VA that returned to its baseline level, that is, before the occurrence of the FTMH. However, the VA did not further improve despite the improvement of the macular profile compared with the LMH status. A loss of central cone integrity, as shown by the presence of ellipsoid zone irregularities or fragmentation, may occur in LMH and during its conversion to FTMH. Despite an apparent foveal profile restoration, the foveal function cannot be fully restored by surgery.

Study Limitations

This study has several limitations, including its relatively small sample size. Indeed, patients with LMH usually have a good baseline VA and therefore could not have been examined by OCT before the development of an FMTH or could not have been followed by a specialized vitreoretinal surgeon because no surgery was planned. The follow-up duration was not homogeneous between patients, and the postoperative visual outcomes could have been underestimated. The multicenter and retrospective design of this study did not allow using a standardized imaging protocol, and even if all included cases underwent sequential spectral-domain OCT imaging, it was admittedly challenging to identify parameters that could have been of interest, such as the posterior vitreous status at baseline.

Conclusions

Lamellar macular holes may evolve spontaneously to FTMH. The pathogenesis of these atypical FTMHs could involve a tangential traction from a contractile epiretinal membrane or a progressive alteration of the foveolar architecture secondary to the disruption of the "bouquet des cones centraux" or both. Surgery may be used to close this secondary macular hole and improve vision to the initial level before the occurrence of the FTMH.

Table 3. Clinical and OCT Data of the Study Patients at the Different Follow-up Examinations

Characteristics	LMH	FTMH	Last Follow-up	*P* Value
No. of eyes	20	20	20	–
VA, logMAR (SE)	0.21 ± 0.19 (20/32)	0.61 ± 0.50 (20/81)	0.29 ± 0.23 (20/38)	0.003
Phakic lens status	12 (60%)	9 (45%)	2 (20%)	0.003
ELM disruption	11 (55%)	–	9 (45%)	0.752
EZ disruption	14 (70%)	–	13 (65%)	1.00
IZ disruption	17 (85%)	–	13 (65%)	0.273

ELM = external limiting membrane; EZ = ellipsoid zone; FTMH = full-thickness macular hole; IZ = interdigitation zone; LMH = lamellar macular hole; logMAR = logarithm of the minimum angle of resolution; SE = Snellen equivalent; VA = visual acuity.

Footnotes and Disclosures

Originally received: November 8, 2020.
Final revision: December 22, 2020.
Accepted: December 28, 2020.
Available online: ■■■.

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Presented in part at: the annual meeting of The American Society of Retina Specialists, Seattle, Washington, July 24–26, 2020.

This study was supported by unrestricted grants for publications from the Research to Prevent Blindness Foundation (New York, NY) and the Hess Foundation (Roseland, NJ).

Disclosure(s):
All authors have completed and submitted the ICMJE disclosures form.
The author(s) have made the following disclosure(s): J.-P.H.: Consultant – Alcon, Allergan, Bausch & Lomb, Novartis, Zeiss.

A.M.A.: Consultant – Alimera Sciences, Allergan, Genentech, Novartis, Oxurion, Regeneron Pharmaceuticals; lecture fees – Spark Therapeutics.

A.G.: Personal fees – Bayer Healthcare, Novartis, Thrombogenics.

R.T.: Personal fees – Alcon, Allergan, Bayer Healthcare, Genentech, Novartis, Roche, Zeiss.

E.R.: Consultant – Allergan, Google LLC, Regeneron.

HUMAN SUBJECTS: Human subjects were included in this study. The human ethics committees at the French Society of Ophthalmology approved the study. All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Chehaibou, Hubschman, Rahimy

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Analysis and interpretation: Chehaibou, Hubschman, Gaudric, Tadayoni, Rahimy

Obtained funding: N/A

Overall responsibility: Chehaibou, Hubschman, Gaudric, Tadayoni, Rahimy

Abbreviations and Acronyms:
FTMH = full-thickness macular hole; **LMH** = lamellar macular hole; **logMAR** = logarithm of the minimum angle of resolution; **SE** = Snellen equivalent; **VA** = visual acuity.

Keywords:
lamellar hole, macular hole, vitrectomy, retina.

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