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ORIGINAL ARTICLE



Treatment of Inflammatory Macular Hole: Case Series and Review of Literature

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ABSTRACT

Purpose: To present the success rate of nonsurgical management of full-thickness inflammatory macular hole (IMH)

Method: Retrospective case series of five patients with IMH.

Result: Five eyes from five patients with IMH enrolled in the current case series. All five eyes had successful closure with corticosteroid in the form of topical, periocular, or intravitreal injections. Systemic immunomodulatory treatment was employed for two patients, in addition to local therapy. For local therapy, one patient received topical eye drops, subtenon injection of corticosteroid, and intravitreal injection of combination of corticosteroid and anti-VEGF was performed in two patients. The closed macular hole reopened in one patient after two years, which required pars plana vitrectomy and anatomical and visual success achieved.

Conclusion: Inflammatory macular holes can be closed with non-surgical interventions, although reopening may occur which requires surgery.

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KEYWORDS

Conservative management; full-thickness macular hole; inflammation; ocular injection; uveitis

Macular hole (MH) as a rare sequel of uveitis was initially noticed by Nussenblatt et al.¹ Although the rarity of the condition does not allow for the exact estimation, Liues et al. gave an approximation of 2.5% for the prevalence of uveitic macular holes among uveitis patients.^{2,3} Three mechanisms have been proposed for pathogenesis of IMH, including an antero-posterior traction, tangential vitreous traction, and inner retinal layer weakness.⁴ Vitreous body inflammation triggers liquefaction and subsequent posterior vitreous detachment (PVD) and associated antero-posterior traction. Meticulous examination of macular holes that develop after occurrence of PVD often reveals that a thin roof covers the macular hole. Epiretinal membrane (ERM) which frequently forms in patients with uveitis is responsible for tangential traction.

In the presence of cystoid macular edema (CME), separation of inner layer of Muller cells from the outer nuclear layer in foveola occurs which lead to a tissue disruption and subsequent full thickness macular hole (FTMH) formation.⁵ Longstanding or recurrent presence of cysts in macula can weaken the retinal structure and predispose to MH formation.^{4,6–8}

Despite having similar mechanisms of evolution with idiopathic macular hole (IMH), it is plausible that the inflammatory macular hole (IMH) has some differences in approach and prognosis. Especially considering the younger age of patients with IMH, there may be a more guarded prognosis. Retinochoroidal atrophy and macular ischemia in the setting of chronic posterior uveitis is an explanation for the poor visual recovery after surgery in these patients.⁷

Here, we report five patients with IMH, successfully treated with local and systemic anti-inflammatory medications.

Case 1

A 60-year-old female presented with visual obscuration in both eyes for the past one and half years. In slit-lamp examination, trace cells were observed in the anterior vitreous of both eyes. BCVA was 3/10 in the right eye and 2/10 in the left eye. In fundus examination, occluded retinal vessels in the inferior arcade and pale optic disc were evident.

Scattered preretinal hemorrhage was observed in the periphery (Figure 1(a, b)).

Due to the presence of signs of inflammation in fluorescein angiography (Figure 1(c,f)), and non perfusion area of retina, the diagnosis of occlusive vasculitis was established and azathioprine and cyclosporine were commenced for the patient. OCT demonstrated a full-thickness macular hole in both eyes, which was larger in the left eye (Figure 1(d, e)). Intravitreal injection of corticosteroid and bevacizumab was performed for her both eyes. In three months follow up, holes were closed in both eyes (Figure 1(h, i)). Systemic immunomodulatory treatment (IMT) was continued for the patient. Two years later, the patient presented with the complaint of central scotoma in the left eye. Recurrence of FTMH was evident in Optical coherence tomography (OCT), which failed to respond to intravitreal injection of corticosteroid and bevacizumab (Figure 2(a, b)). The patient was scheduled for pars plana deep vitrectomy, internal limiting membrane (ILM) removal, and SF6 injection for this eye. Holes remained closed in both eyes in four years follow-up (Figure 2(c, d)).

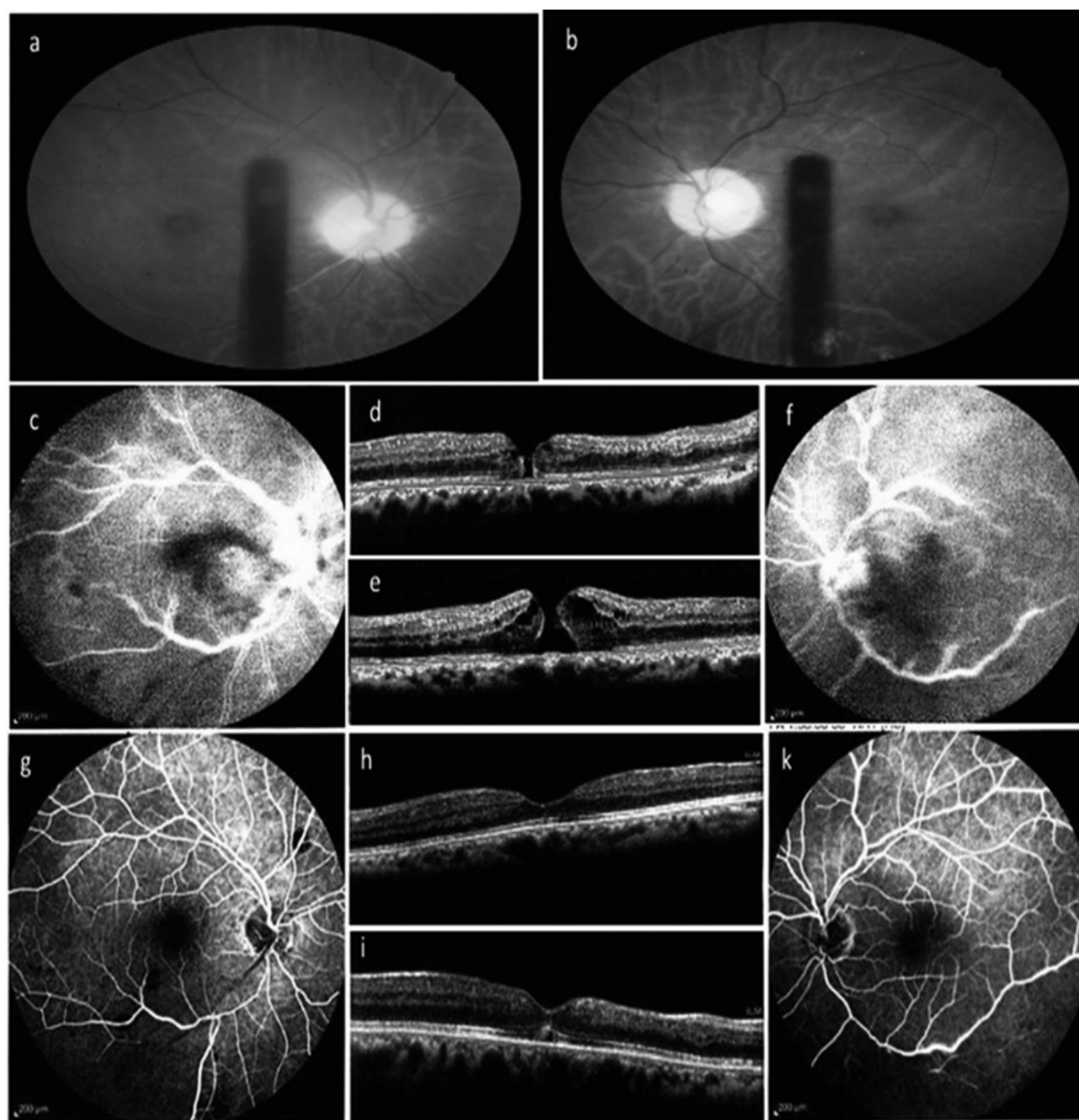


Figure 1. Color fundus photographs of the right and left eyes (a, b) inferior branches of retinal vessels are occluded with pale optic nerves in both eyes. A full-thickness macular hole is evident in the left eye (a). Fluorescein angiography illustrates retinal ischemia inferotemporally in both eyes. Vascular leakage along superior and inferior arcade as well as optic nerve leakage are evident in both eyes (c,f). Optical coherence tomography (OCT) reveals small intraretinal cysts and full thickness macular hole which is larger in the left eye (d,e). Three months after the injection of intravitreal corticosteroid and antiVEGF for both eyes and starting the immunomodulatory agents, FA of both eyes shows dramatic improvement in vascular leakage. The ischemic areas along the inferior arcade persist (g,k). OCT reveals closure of hole in both eyes, some outer retina defect can be appreciated (h,i).

Case 2

A 65-year-old male was referred to the clinic with the chief complaint of decreased visual acuity in the left eye. BCVA was 1/10 in this eye and slit-lamp examination revealed 1+ cell in the anterior vitreous according to the Standardization of Uveitis Nomenclature (SUN) classification. OCT demonstrated the epiretinal membrane and FTMH in the left eye (Figure 3(a)). FA in both eyes showed optic nerve leakage and petaloid leakage in the macular area (Figure 3(c-f)) confirming the posterior pole inflammation.

Subtenon injection of triamcinolone was performed for the left eye and weekly oral methotrexate was started for the patient. Despite the presence of epiretinal membrane, the macular hole was closed within one month after injection, and the hole remained close in his last follow up (Figure 3(b)). IMT was maintained and cells in vitreous cavity improved with no flare up.

Case 3

A 52-year-old man with a history of hypertension referred to the clinic with photophobia and decreased vision in the left eye

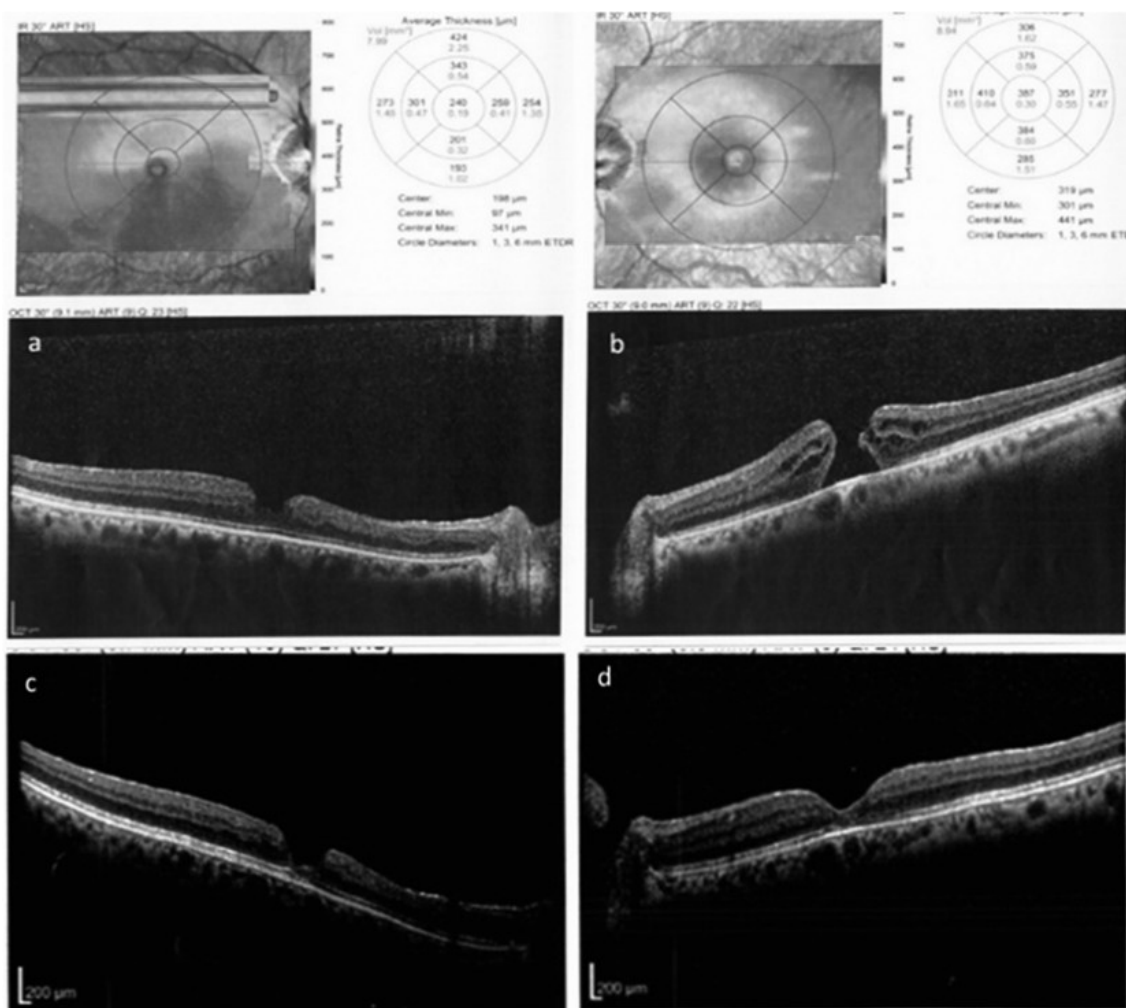


Figure 2. Two years later, OCT shows a lamellar macular hole in the right eye (a) and a full-thickness macular hole in the left eye (b). Map reveals retina thinning especially in inferior arcade of both eyes, compatible with an old vascular occlusion in inferior arcade in both eyes, which is correspondent to inner retina thinning in OCT. Postoperatively, OCT shows macular hole closure in the left eye which remained stable at last follow up in 4 years (c,d).

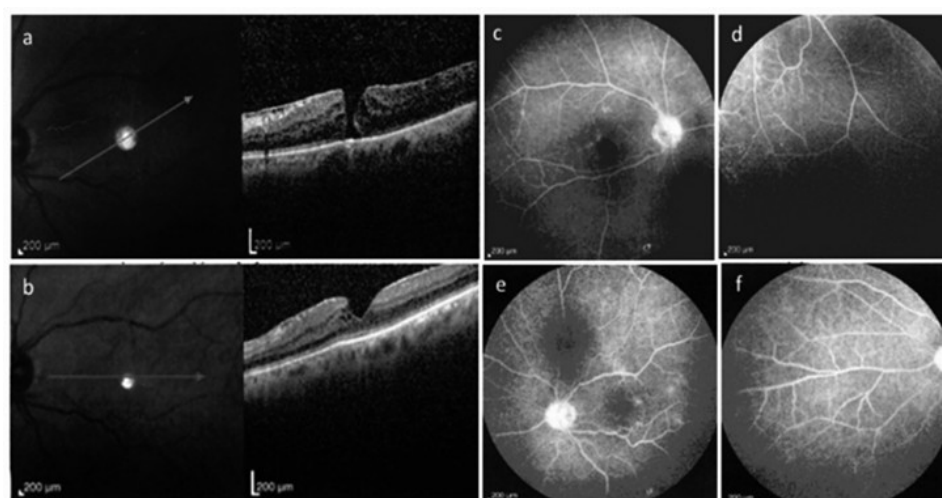


Figure 3. OCT of the left eye demonstrate a full thickness macular hole and epiretinal membrane. Cysts of Intraretinal fluid can be observed as well (a). FA of both eyes show optic nerve leakage and mild capillary leakage in both eyes (c,d,e,f). Left bottom image shows closure of the hole five months after pericardial corticosteroid injection with substantial improvement of retinal edema and some residual cystic fluid in the vicinity of foveal pit (b).

for the past three days. On clinical examination, the best-corrected visual acuity (BCVA) of the right and left eyes were 10/10 and 4/10, respectively. In slit-lamp examination, 2+ cells

in the anterior chamber and 1+ cell in the vitreous cavity were evident in the left eye. Intraocular pressure was normal and fundus examination and OCT revealed a FTMH in the left eye.

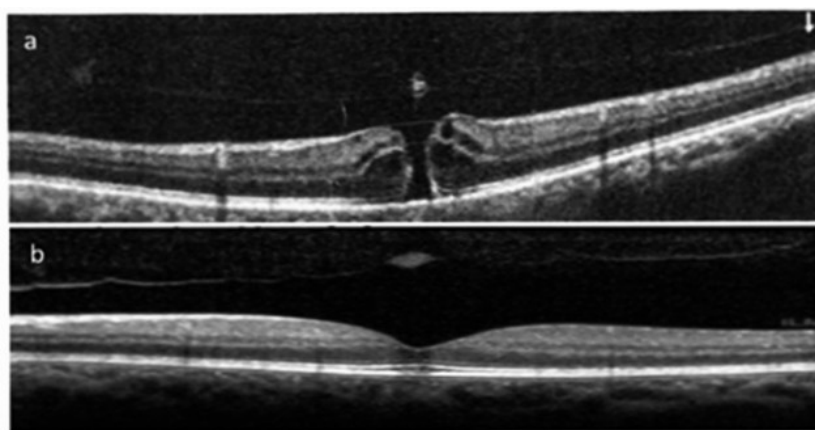


Figure 4. Macular SD-OCT of the left eye reveals full thickness macular hole with uveitic cystic edema. Retinal thickening in the edges of macular hole is caused by cysts which pushed foveal borders away. An operculum is evident as a hyperreflective dot above the hole in line with a detached posterior hyaloid face defined with a white arrow. (a) Complete closure of the hole two months after using topical corticosteroid, NSAIDs and carbonic anhydrase inhibitor. The operculum is still evident in line with detached posterior hyaloid face. The cysts in the edges of macular hole resolved completely (b).

In OCT, intraretinal cystic spaces surrounding the walls of the hole could also be recognized. Ophthalmic examination of the right eye was unremarkable.

This was the first attack of uveitis in this patient. Two months after applying topical betamethasone, dorzolamide, ketorolac, and homatropine, the patient's BCVA improved to 8/10, and on follow-up OCT imaging, FTMH was completely closed in this eye. Subtle irregularity was seen in the outer retinal layers in the fovea with an operculum seen as a hyperreflective material in line with the posterior hyaloid face above the fovea. In subsequent follow-ups, the patient's BCVA improved to 10/10 and the uveitis episode subsided completely (Figure 4(a, b)).

Case 4

A 57-year-old lady presented to the clinic with the complaint of decreased visual acuity of the right eye. BCVA of the right eye was 4/10. We observed cells in vitreous cavity and prescribed subtenon injection. Patient did not consent to the

injection. In two months referral to the clinic, the hole has closed spontaneously with improvement of inflammation (Figure 5(a, b)).

Case 5

A 56 years old female underwent scleral buckling for the repair of retinal detachment in the left eye. The surgery was successful and the retina was reattached. Subsequently, she was found to have postoperative CME (Figure 6(a)) for which she received an intravitreal injection of bevacizumab with some improvement. Ten months later, she developed a FTMH in this eye (Figure 6(b)). Intravitreal injection of corticosteroid and bevacizumab was performed, resulting in the closure of the macular hole which was evident in OCT, two months after the injection (Figure 6(c)). Baseline VA after retinal reattachment by scleral buckling was 5/10 that approached 7/10 after anatomical closure of the hole.

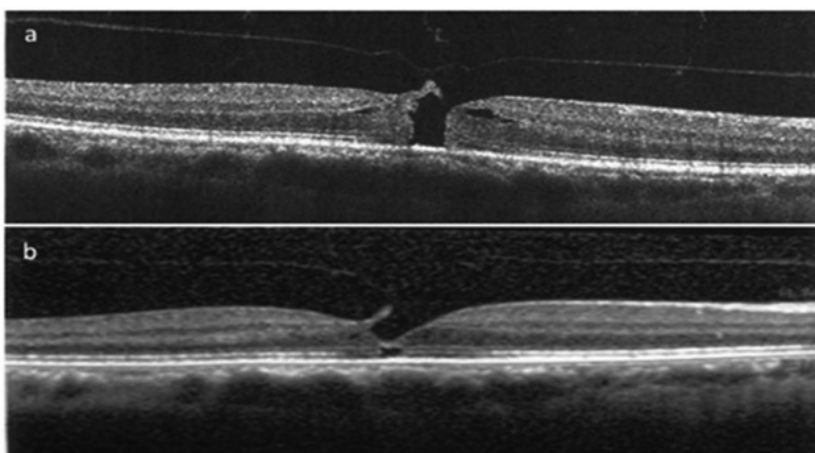


Figure 5. Macular OCT of the right eye reveal full thickness macular hole with posterior hyaloid face seems to retain some fibrillar attachment to retinal flap of hole in fovea. Cysts are present in the edges of macular hole located in outer plexiform and inner nuclear layer (a). Two months after, OCT illustrates closure of macular hole in the right eye. A small outer lamellar hole involving the ellipsoid zone is apparent. The same fibrillar attachment persists after macular hole closure. The cysts in parafoveal area resolved completely (b).

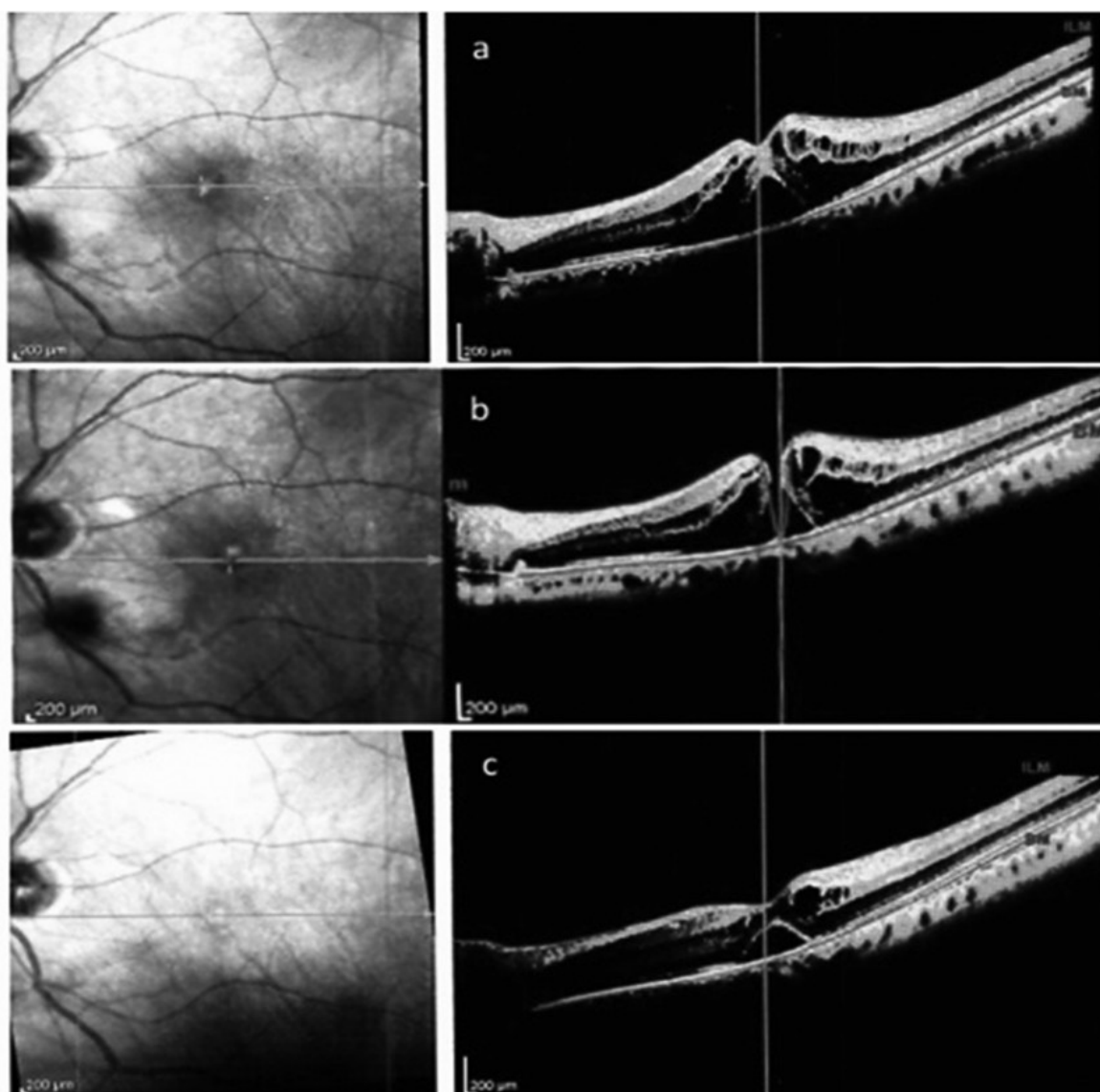


Figure 6. OCT of the left eye shows post-operative CME that occurred after scleral buckling surgery (a), persistent CME lead to formation of a full thickness macular hole (b). Two months after the intravitreal injection of corticosteroid and anti VEGF, macular hole has been closed with residual cysts and subretinal fluid in macula. Thickness of fovea has decreased.

Discussion

A review of the literature revealed 55 cases of posterior uveitis associated macular hole, 35 cases were related to Behcet's disease. Few reports are existing in the literature regarding the management of the IMH.^{2,4,9-17}

While the exact mechanism of IMH formation remains to be elucidated, several factors have been suggested, including PVD induced by inflammation, vitreoretinal traction, ERM, unroofing of CME cavities, and outward displacement of retinal tissue. Pushing forces exerted by volume occupying cystoid spaces alters the foveal contour orientation causing an outward displacement of foveal edges and disruption of retinal tissue. This component is the main contributing factor in inflammatory and postocular surgery MH. Bhatnagar et al. showed that post-cataract surgery CME is associated with a seven-fold increase in the risk of reopening of macular hole.¹⁸

Hayashi et al. introduced a patient with four recurrences of IMH. Retinal protrusion at the edge of the hole was

observed during recurrences and bridging tissues at the time of closures. While vitrectomy was performed twice to address the macular hole in their case, topical corticosteroid drops helped closing the macular hole in the rest of episodes. In fact, cessation of these drops was the underlying cause of one of the episodes. They hypothesized that protrusions mediate outward migration of retinal tissue and contradictory movement may be caused by bridging tissues.^{17,19,20} It has been shown that lack of pumping function of RPE may also contribute to IMH formation.²¹ Shukla et al. reported a case of IMH, not closed after vitrectomy, which was successfully closed with posterior subtenon injection of triamcinolone acetate.²² The authors proposed that the presence of intraretinal cystoid spaces in addition to subretinal fluid in the absence of any evidence of traction on the retina supports the role of inflammation in MH formation in their case. They concluded that observing these signs suggests macular edema associated uveitis may contribute to MH formation.²³⁻²⁵

One can conclude that bouts of inflammation can reopen the macular hole and addressing inflammation can be helpful to reverse the situation and help closing the macular hole. Similar to our first case, IMH may finally need operation after prior successful treatment with anti-inflammatory agents; or similar to the reported cases, the role of inflammation may remain unnoticed even after surgical intervention. The option of anti-inflammatory agents is still on the table for the management of the hole. Of note, any intraocular manipulation can potentially induce inflammation, macular edema, and macular hole formation. Clinical suspicion and fluorescein angiography can be helpful in discovering inflammation in subclinical cases.

The optimal treatment for inflammatory MH is not established yet. A recently published interventional case series (20 eyes) showed the efficacy of vitrectomy and ILM peeling in management of this condition. A high rate of anatomical success of 81% was achieved, while holes in three eyes reopened within one month after surgery; in two the second surgery had successful results. The hole in one eye, despite two surgeries, never achieved anatomical closure. This patient had the most prolonged duration of uveitis.¹⁴

Considering that vitrectomy is an invasive procedure that can promote further inflammatory response, it is preferred to manage IMH with the least manipulative manner.²⁴ Of note is proper medical control of inflammation prior to ocular surgery such as vitrectomy that was ignored in more than half of cases.^{2,14}

Mechanism behind the closure of IMH with anti-inflammatory agents is not well understood. One hypothesis is that in those with CME, when retina gets dry with the use of corticosteroids, the edges of separated retina can reappose, resume its integrity and repair the hole.²⁵ It is plausible that such closure is more frequently seen in smaller holes. In our second case, epiretinal membrane did not interfere with macular hole closure. In fact, in some references, the presence of a contractile epiretinal membrane has been considered a contributory factor in macular hole closure.²⁶ Activation of Muller cells and glial cell proliferation in inner retina and formation of bridging tissues have also been considered as mechanisms in spontaneous macular hole closure. Our fourth case showed spontaneous closure of IMH.

Intraocular injections of medications can affect the vector of vitreoretinal interface tractions, if any, and this may be another factor contributing to the closure of IMH.

While the standard treatment for IMH is pars plana vitrectomy, successful management of IMH can be achieved with minimally invasive interventions that can control the inflammation such as topical or systemic anti-inflammatory agents as well as periocular or intraocular steroid injections.

Ophthalmologists should be vigilant for any sign of intraocular inflammation, to choose the best treatment option for IMH. It should be born in mind that the minimally invasive procedure be tried initially. As uveitis has a propensity to recur, a closed IMH is at the risk of reopening especially in bouts of reactivation of the underlying inflammation. More invasive procedures such as vitrectomy should be considered as the last resort and in the setting of a controlled intraocular inflammation.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper

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Spontaneous closure of a traumatic macular hole: The fastest yet?

Oscar Eaton¹, Francesc March de Ribot^{1,2}

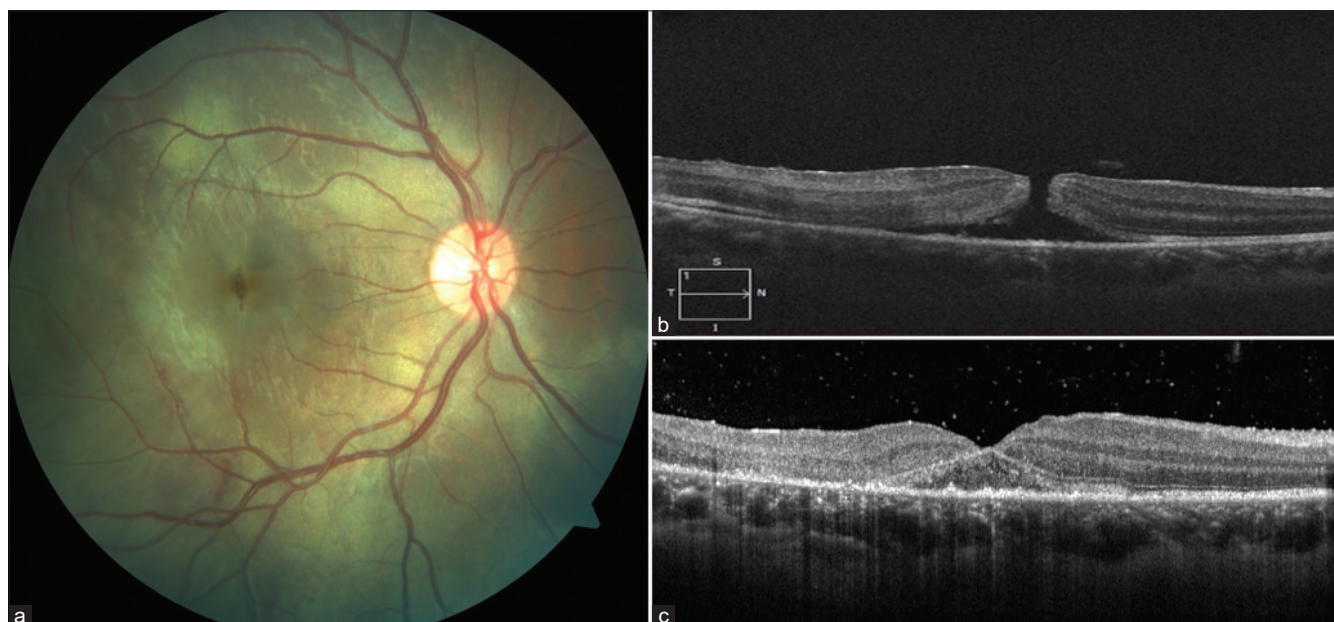


Figure 1: (a) Color photograph of the right fundus at 4 h after the trauma, showing a full-thickness macular hole surrounded by retinal edema. Original image. (b) OCT horizontal axis image demonstrating base width 1969 μm and narrowest width 148 μm . Original image. (c) OCT demonstrating closure of macula hole at day 4. Original image. OCT = optical coherence tomography

Key words: Macular hole, spontaneous closure, traumatic

A man in his 20s presented to our eye department following blunt trauma to the right eye from a paint ball gun earlier that day. The visual acuity (VA) of the affected eye was 1/60, the intraocular pressure (IOP) was 14 mmHg, and the anterior segment was normal. Posterior segment

examination revealed a full-thickness elliptical macular hole with perimacula edema and scattered intraretinal hemorrhage and edema throughout the periphery [Fig. 1a]. On ocular coherence tomography (OCT), the narrowest internal diameter of the defect measured 148 μm [Fig. 1b]. There was presence of vitreomacular adhesion with overlying operculum, localized detachment of the neurosensory retina, and absence of cystic edema at the hole margin [Fig. 1b]. On review 4 days after injury, spontaneous closure was observed [Fig. 1c]. The examination revealed complete posterior vitreous detachment with apposition of the macular hole, increased retinal thickness, and atrophic changes. The patient was reviewed again at 3 months and the VA was found to be 1/60. There was restoration of the foveal pit and progression of the inferotemporal macular atrophy.

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Discussion

Spontaneous closure of traumatic macular holes has been reported many times before, with a varied time course of between 2 and 54 weeks.^[1,2] Closure under 2 weeks is rare, with the earliest reported being 10 days.^[3] Classification of traumatic macular hole based on OCT findings can aid in the prediction of hole closure.^[4] In this case, the absence of posterior vitreous detachment at the time of injury and the absence of cystic edema at the hole margin were associated with hole closure. Spontaneous closure is usually associated with improvement in VA,^[5] although the severity of initial trauma and the extent of neurosensory retinal detachment can limit the visual outcome, as in this case.

Patient consent

Oral consent has been obtained to allow publication of the case and inclusion of imaging.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published

and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Spontaneous Closure of a Full-Thickness Macular Hole

Some macular holes may resolve with observation in the setting of epiretinal proliferation and dry AMD.



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KEY TAKEAWAYS

- Based on its characteristics and presentation on OCT, a full-thickness macular hole (FTMH) may resolve without vitrectomy, suggesting initial observation may be prudent in select cases.
- Characteristics of FTMH that may suggest spontaneous closure include epiretinal proliferation (EP) and drusenoid deposits seen on OCT.
- In this case, the patient demonstrated EP based on the homogenous material of medium reflectivity anterior to the retinal nerve fiber layer, which seems to have aided in FTMH closure.

Visual deterioration due to an untreated full-thickness macular hole (FTMH) impairs quality of life for many patients. Surgical intervention is the mainstay treatment for most FTMHs; Tognetto et al found that vitrectomy performed less than 6 months from presentation leads to better anatomic outcomes and visual improvement.¹ Moreover, it is commonly believed that late intervention is a risk factor for surgical failure; thus, many retina specialists tend to intervene earlier rather than later.

The spontaneous closure rate for a stage 2 MH has been reported as 11.4%,^x with the rates for stage 3 and stage 4 being closer to 4%, suggesting spontaneous closure is infrequent.² However, based on its characteristics and presentation on OCT, a FTMH may resolve without vitrectomy. Various factors contribute to spontaneous closure, such as the stage of the MH, size or presence of bridging retinal tissue, epiretinal membrane, underlying pathogenesis, and vitreomacular traction (VMT). Spontaneous closure of a FTMH has also been described in patients with juxtafoveal telangiectasis (JXT),³ as well as in patients with epiretinal proliferation (EP).⁴

Our case study shows closure of a FTMH in the presence of EP and intermediate dry AMD with subsequent atrophy, suggesting clinicians should consider close observation for FTMH, depending on OCT characteristics.

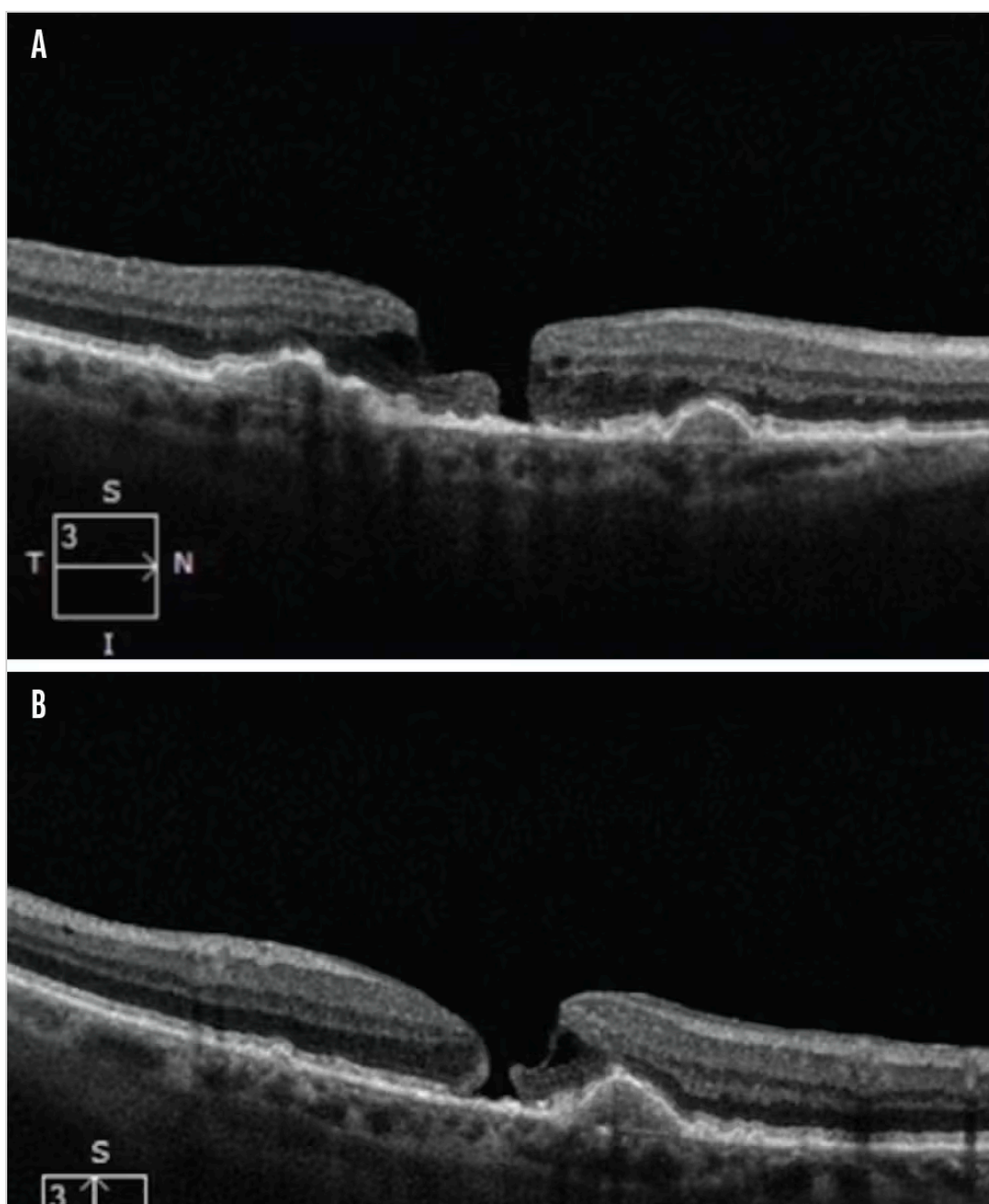


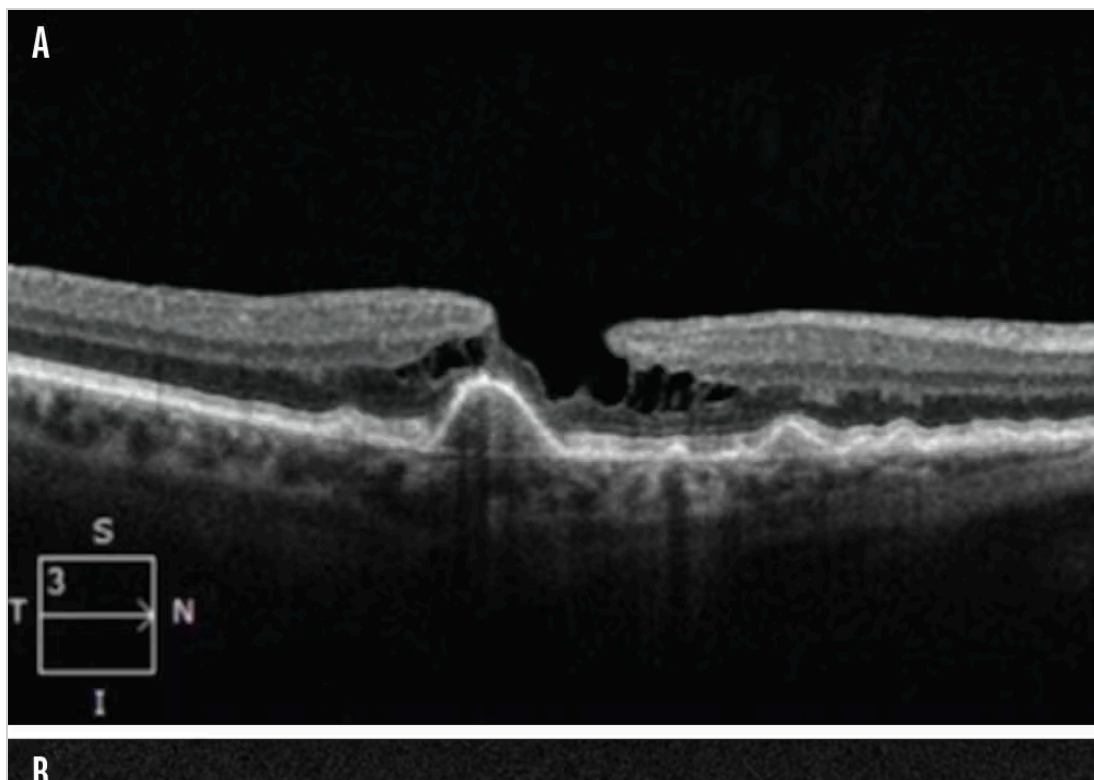


Figure 1. On SD-OCT at initial presentation, both the horizontal (A) and vertical (B) scan through the fovea showed a FTMH with EP and underlying drusen without subretinal fluid in the patient's right eye.

CASE REPORT

A 74-year-old man with hypertension, hyperlipidemia, and arthritis presented to the clinic for a 4-week follow-up appointment for blurred vision and floaters in the right eye. On examination, his BCVA was 20/50 OD. A dilated fundus examination of his right eye showed a posterior vitreous detachment, retinal arteriovenous nicking, a new FTMH, and many large drusen without hemorrhage.

Spectral-domain OCT (SD-OCT) illustrated EP and a FTMH with underlying drusen without subretinal fluid in his right eye (Figure 1). SD-OCT performed 45 days later illustrated resolution of the FTMH (Figure 2). One year after initial presentation with the FTMH, SD-OCT demonstrated collapse of the temporal and superior drusen along with outer retinal atrophy (Figure 3). It's worth noting that with the outer retinal atrophy, the retinal pigment epithelium (RPE) appears to remain intact in the locations of drusen collapse. Sequentially tracked SD-OCT, obtained over the following 4 years, continued to demonstrate resolution without recurrence of the FTMH. The patient's final VA was 20/80-1 OD.



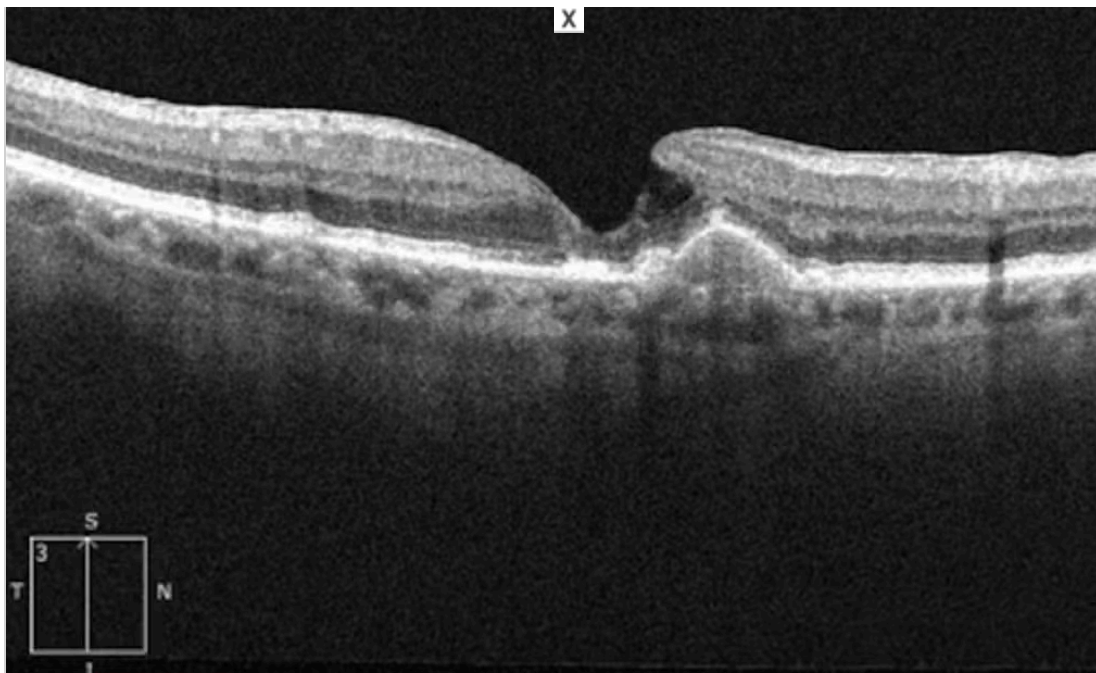


Figure 2. Forty-five days after initial presentation, the horizontal (A) and vertical (B) scans through the fovea showed resolution of the FTMH with persistent subfoveal drusen.

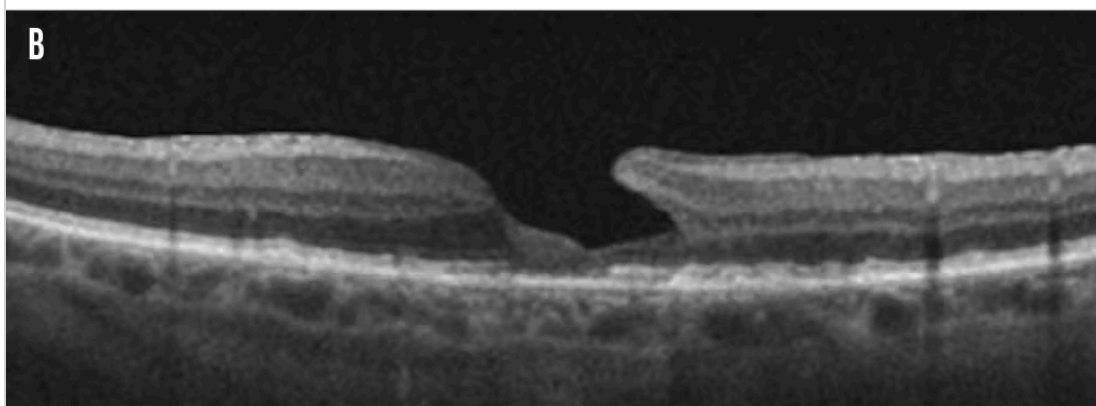
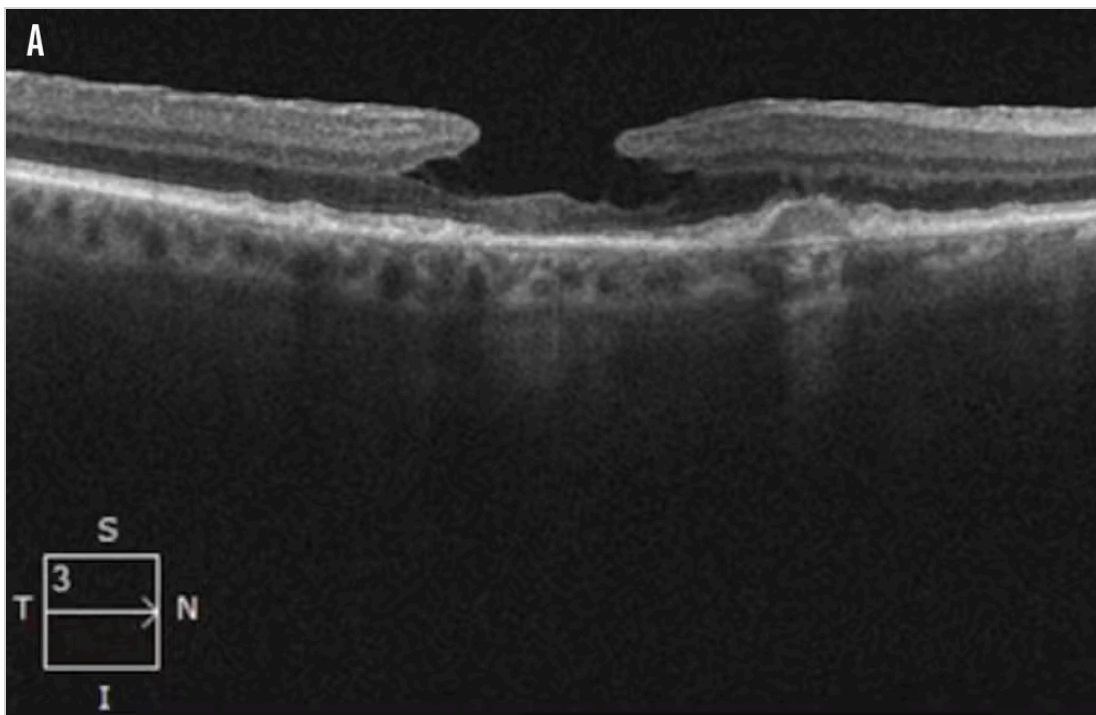




Figure 3. One year after initial presentation, the horizontal (A) and vertical (B) scans through the fovea showed continued resolution of the FTMH, as well as outer retinal atrophy and collapse of previous drusen.

CONDITIONS FOR SPONTANEOUS CLOSURE

Spontaneous closure of a FTMH is uncommon, with a rate between 0% and 6%.⁵ The average time for spontaneous closure is about 3 months.⁶ The pathophysiology for spontaneous closure is not well understood, but Privat et al suggested the release of VMT may account for MH closure, which is also the reasoning behind performing vitrectomy.⁵ However, the patient in our case already had a posterior vitreous detachment at presentation and, therefore, no VMT, suggesting another etiology for closure.

The concept of spontaneous FTMH closure has been seen in other conditions, such as JXT. In JXT, it is believed that Müller cell degeneration causes neural retina loss and vascular abnormalities.³ Müller cells serve several important roles in the health of the retina, particularly structural integrity; therefore, Müller cell loss is thought to contribute to diminished structural support, leading to MH formation.⁷ Although Müller cells can contribute to macular hole formation, Bringmann et al suggests that residual or reactive Müller cells may paradoxically allow for spontaneous closure through glial proliferation and repair of foveal structure once tractional forces are relieved. The mechanism of this can be explained by bridging the gap in the inner portion of the central outer nuclear layer, forming a new inner Müller cell layer, and restoring the external limiting membrane.⁸

EP may have also played a role in our case. While EP is not completely understood, it may be due to Müller cell proliferation and migration from the inner retinal layers, vitreous components, and RPE cell proliferation and migration through ellipsoid zone defects.^{4,9} EP may be associated with weak contractile properties that may prevent FTMH closure.⁹ However, our patient demonstrated EP based on the homogenous material of medium reflectivity anterior to the retinal nerve fiber layer, which seems to have aided in FTMH closure.

Our case is accompanied by progressive collapse of drusen after hole closure. In the literature, there

are four case reports and one case series of two patients with FTMH with either subfoveal soft drusen or pigmented epithelial detachment who underwent surgical closure of FTMH that also resulted in improvement or complete resolution of drusen and/or pigmented epithelial detachment.¹⁰ The resolution of the drusen following retina surgery is thought to be due to phagocytosis of drusen by macrophages that may be further enhanced by internal limiting membrane peeling.¹⁰

In our case, spontaneous resolution of the FTMH occurred with subsequent atrophy of the drusen. It has been speculated that eyes with outer retinal pathology (eg, AMD) might have a higher rate of EP formation.¹¹ The relationship between drusen collapse, development of outer retinal atrophy (ie, incomplete RPE and complete RPE atrophy and outer retinal atrophy), EP, and FTMH is still unclear and should be evaluated further in the setting of intermediate AMD.

Lastly, topical therapies consisting of steroids, carbonic anhydrase inhibitors, and nonsteroidal antiinflammatory drugs have been used off-label for closure of MHs.¹² These agents tend to work well for smaller MHs and in patients with little or no edema with a more than 50% success rate.¹² The mechanism by which topical agents work is thought to involve decreasing macular edema, leading to closure of the hole by bringing the edges together.¹² As our patient did not have any macular edema or subretinal fluid, had relatively preserved vision, and demonstrated MH closure during subsequent follow-up visits, further treatment has not been pursued. However, topical agents remain a reasonable option to consider for smaller holes with minimal or absent edema and relatively preserved vision, particularly before considering more invasive intervention.

TAKE STOCK OF OCT FINDINGS

The current treatment for FTMH is vitreoretinal surgery, but certain circumstances may lead FTMHs to resolve spontaneously, suggesting initial observation may be prudent in such cases. Characteristics of FTMH that may suggest spontaneous closure include EP and drusenoid deposits seen on OCT. More research is needed to evaluate the course of FTMH in this setting.

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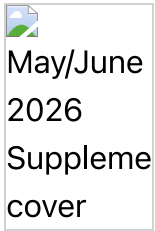
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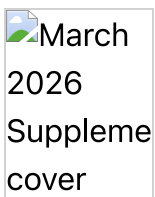
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How to recognize predictors of spontaneous macular hole closure

A review of anatomical characteristics of holes more likely to close without surgery and noninterventional management options.



By Loka Thangamathesvaran, MD, and J. Fernando Arevalo, MD, PhD

DECEMBER 23, 2024

Take-home points

- Anatomic features of macular holes are important to take into consideration when evaluating which full-thickness macular holes (FTMH) will undergo spontaneous closure.
- A combination of topical steroids, carbonic anhydrase inhibitors, nonsteroidal anti-inflammatory drugs and anti-VEGF agents have been used in the management of FTMH closures.
- It's important to plan for surgery early in the treatment course to ensure no delays in the event observation or nonsurgical interventions don't work.



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Full-thickness macular holes are complete defects in the neurosensory retina that are a result of multiple etiologies, including, but not limited to, vitreomacular traction, trauma, retinal detachment or uveitis. The pathophysiology of the most common etiology, VMT, includes a tractional force resulting in localized thinning of the retina that causes a progressive defect with complete loss of retinal tissue.¹

Conventionally, the most definitive management of full-thickness macular hole (FTMH) has been pars plana vitrectomy with or without internal limiting membrane peel and tamponade with gas or silicone oil. However, these interventions present challenges, including complications such as cataract, risk of retinal detachment and the need for face-down positioning.

Bios

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DISCLOSURES: The authors have no financial relationships to disclose.

Although spontaneous hole closure has traditionally been observed with traumatic macular holes, with closure rates ranging from 10 to 50 percent, and reports recommending observation for up to four months to see if traumatic holes close, newer studies are finding spontaneous closures with observation and nonsurgical interventions in non-traumatic FTMH.²

This article will review anatomical characteristics of holes that are more likely to spontaneously close, variations in the noninterventional management options, and how to predict which holes will need surgery once these interventions are put in place.

Imaging markers of spontaneous FTMH

Our group studied imaging features associated with closure of FTMH.³ The retrospective study included cases with an established diagnosis of FTMH, as determined by spectral-domain optical coherence tomography, that were followed without surgery and collected from retina specialists worldwide. Successful closure was defined as flattening and reattachment of the hole rim along the entire circumference of the hole.

Exclusion criteria included presence of retinal dystrophy, foveoschisis, neovascular age-related macular degeneration and history of vitreous surgery less than one year prior. SD-OCT scans were reviewed for macular parameters including apical diameter, narrowest diameter, basal diameter and height (*Figure 1*).

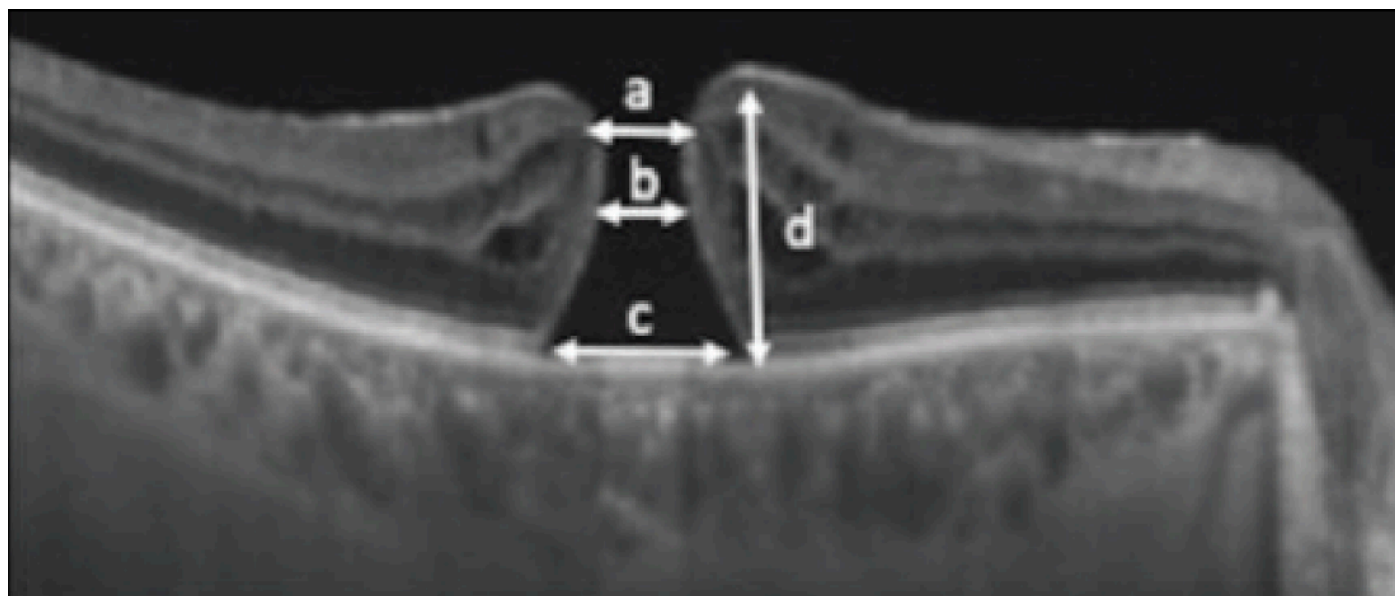


Figure 1. A diagram of full-thickness macular hole parameters: a = apical diameter; b = minimum diameter; c = basal diameter; and d = height. (Reprinted with permission from Uwaydat SH, Mansour A, Ascaso FJ, et al. *Clinical characteristics of full thickness macular holes that closed without surgery.* *Br J Ophthalmol.* 2022;106:1463–1468.)³

Additional FTMH parameters that we evaluated include macular hole index (height/basal diameter), diameter hole index (DHI, an indicator of tangential traction defined as narrowest diameter divided by basal diameter), tractional hole index (THI, an indicator of anteroposterior traction and retinal hydration defined as height/narrowest diameter) and subretinal fluid volume.

Researchers in Spain previously evaluated these markers as potential predictors of successful outcomes in FTMH surgery. They identified a narrowest diameter for smaller macular hole and a larger tractional hole index as predictive factors for a good visual prognosis after surgery.⁴

SD-OCT parameters that characterized the vitreoretinal interface included the presence of vitreomacular traction in 12 (15.8 percent) eyes, perifoveal PVD in 42 (53.8 percent), foveal epiretinal membrane in 10 (12.8 percent), cystoid macular edema in 49 (62.8 percent) and subretinal fluid in 20 (25.6 percent).

In our study, the FTMH closed in 74 eyes of 78 patients. On multivariate analysis, initial visual acuity correlated to the height and narrowest diameter of the hole while final visual acuity correlated with the basal diameter. Time for closure of FTMH was a median of 2.8 months and correlated to the narrowest diameter and the presence of subretinal fluid. THI negatively correlated with time to closure.

Other studies of spontaneous closure

Other studies that examined characteristics of spontaneous closure found an association of faster closure rates when CME was present because the edema helps reapproximate the hole edges by a mechanism of primary intention.^{5,6} This might play an important role in the management of FTMH associated with uveitis.

A study this year by Jessie Wang, MD, and colleagues, identified factors associated with decreased rates of spontaneous closure, which included increasing hole size, as every 10 μm decrease in size correlated to an increase in closure by a factor of 1.2.⁷ The study also highlighted the presence of VMT related inversely to successful closure.

The study further corroborated this with the finding that patients who had undergone vitrectomy had higher closure rates due to the absence of tractional forces. Furthermore, the study found that the best-corrected visual acuity was better in patients whose holes closed with only topical drops compared to holes that required PPV. However, the holes that underwent PPV were significantly larger and had persistent VMT, which could also affect final visual acuity. However, there were no differences in BCVA between patients that underwent surgery after drops vs. surgery at the initial presentation.⁷

Agents used for FTMH closure

In our retrospective observational series, 18 eyes received the following nonsurgical interventions, with some eyes receiving multiple interventions: intravitreal anti-VEGF agents (four eyes); topical corticosteroids (13); and topical nonsteroidal anti-inflammatory drugs (seven). We didn't compare these modalities.

Other studies have used a combination of these modalities, with Dr. Wang's group using this standardized regimen:

- topical steroids prednisolone acetate 1% every six hours or difluprednate 0.05% every six to 12 hours;
- NSAIDs ketorolac tromethamine 0.5% or bromfenac 0.07% every six to eight hours; and
- carbonic anhydrase inhibitors (CAIs) brinzolamide 1% or dorzolamide 2% every eight to 12 hours.⁷

In a multicenter U.S. study, participants were started on the following regimen:

- off-label topical prednisolone acetate 1% every six to eight hours or difluprednate 0.05% every eight to 12 hours;
- ketorolac-tromethamine 0.5% every six to eight hours or bromfenac 0.07% every six to 24 hours; and
- brinzolamide 1% or dorzolamide 2% every eight to 12 hours.⁵

No studies have yet compared the efficacy of these different drop regimens.

Dynamic predictors of FTMH closure

In our study, the mean time to closure from initial detection was 6.2 months with a mean logMAR initial ($\pm$ standard deviation [SD]) visual acuity improved from 0.65 ± 0.54 to 0.34 ± 0.45 (Snellen equivalent 20/89 to 20/44). The initially closed FTMH reopened in seven eyes (9 percent) after a mean of 8.6 months.

Among the eyes that reopened, two closed and one stayed open after vitrectomy, and one closed on topical steroids and topical NSAIDs. Four eyes had no surgery. A total of 74 eyes had stable or improved final vision, while four eyes lost vision due to a subfoveal scar after blunt trauma (two eyes) and foveal RPE atrophy (two eyes). Three FTMH resolved after VMT resolution and three closed after a new occurrence of PVD. One FTMH closed despite the persistence of VMT.

Mean time for closure was:

- 1.6 months for eyes with trauma;

- 4.3 months for eyes without trauma but that had therapy for CME;
- 4.4 months for eyes without trauma and without therapy if the holes were $<200\text{ }\mu\text{m}$ in size; and
- 24.7 months for holes $>200\text{ }\mu\text{m}$.

Figure 2 shows a case of a patient that had sustained a sports-related injury and started on topical NSAIDs, with hole closure resulting in visual acuity improvement from 20/40 to 20/20.

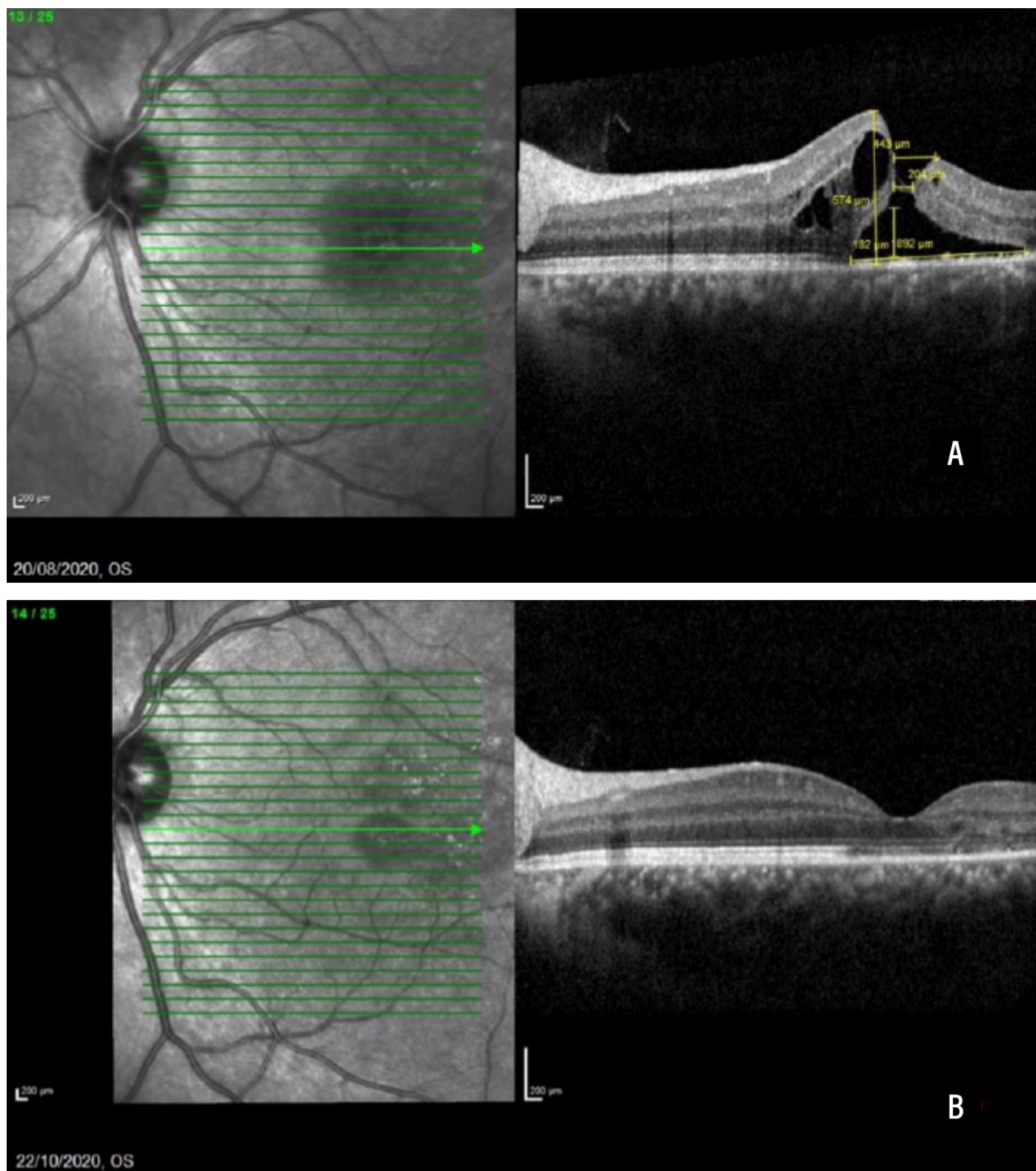


Figure 2. Spectral-domain optical coherence scans before full-thickness macular hole closure (A) and two months after closure (B). This 24-year-old White male sustained a sports injury and was started on topical NSAID. Visual acuity improved from 6/12 (20/40) to 6/6 (20/20). (Reprinted with permission from Uwaydat SH, Mansour A, Ascaso FJ, et al. *Clinical characteristics of full thickness macular holes that closed without surgery. Br J Ophthalmol.* 2022;106:1463–1468.)³

Dr. Wang's group noticed that when tracking the progression of FTMH size over time, the eyes that responded to drop therapy showed a rapid reduction in size. In particular, rates of macular hole narrowing and reduction in central foveal thickness acted as indicators for drop effectiveness.⁷ In total 36.7 percent of patients achieved hole closure; however, final visual acuity didn't differ between eyes undergoing primary PPV vs. those taking drops before undergoing PPV. The study didn't report on reopening of FTMH.

In the multicenter U.S. study, OCT studies showed decreased cystoid changes within two to four weeks and FTMH closure with visual acuity improvement in two to eight weeks in most eyes. The median treatment duration until initial closure was approximately 5.6 weeks. Total duration of drop treatment, including taper, ranged from 3.5 to 20 months. Two patients had FTMH recurrence at six months after an initially successful closure, and two others subsequently needed PPV for visually significant epiretinal membrane.

Anatomical markers

These studies highlight the anatomical characteristics that are important when considering which FTMH are more likely to spontaneously close. First, FTMH <200 μm , especially in the setting of trauma and without the presence of VMT, have a high likelihood of closure.⁸ In addition, the absence of VMT is important because persistent tractional forces can overwhelm the RPE pump, preventing hole closure.

These studies also highlight that the use of drops can help improve the closure process without affecting the final outcomes. When comparing closure rates in patients who had FTMH closure vs. those who didn't, the participants who used drops had greater closure rates.^{8,9}

Furthermore, in participants who had successful hole closure rates, there was a significant reduction in macular hole size and changes in SD-OCT markers early on in the treatment, highlighting the importance of close monitoring and quick intervention if there's no response. In particular, Dr. Wang's group recommended scheduling a tentative date for surgery even in the group that initiates drop therapy to prevent any surgical delays. Finally, it's important to review the adverse effects of these topical agents, including corneal melt, ocular surface irritation and elevated intraocular pressure.

FTMH <200 microns, especially in the setting of trauma and without VMT, have a high likelihood of closure. The absence of VMT is important because persistent tractional forces can overwhelm the RPE pump, preventing closure.

Future studies

We need prospective, randomized, double-masked, high-powered studies in the future to improve our clinical management and to help us apply these principles into practice. First, studies that compare different noninterventional therapeutic protocols will be helpful to determine whether individual agents or specific combinations will help promote FTMH closure. This is particularly useful in patients who have contraindications to certain agents, such as topical corticosteroids (in patients with glaucoma) and topical NSAIDs (in patients with corneal surface disease).

Second, knowing how systemic conditions, such as diabetes, affect rate of hole closure can help clinical decision-making. Finally, as artificial intelligence continues to shape how we practice medicine, it will be useful to identify if OCT biomarkers can be put into an algorithm to help predict which patients can be observed and who would need surgery, and then use the dynamic response from their OCT scans to further refine clinical decision-making.

Bottom Line

Not all FTMH require surgery. Careful analysis of SD-OCT markers can help determine which FTMH might close on their own, with close vigilance to treatment response being essential in avoiding lapses in surgical intervention. **RS**

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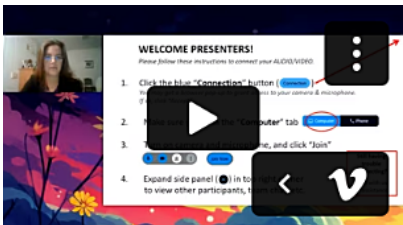


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The time course of spontaneous closure of idiopathic full-thickness macular holes

Jonas Neubauer¹ · Faik Gelisken¹ · Taylan Ozturk² · Karl-Ulrich Bartz-Schmidt¹ · Spyridon Dimopoulos¹

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Abstract

Purpose Spontaneous closure of idiopathic full-thickness macular holes (iFTMH) has been reported regularly. However, little is known about its probability and timeline.

Methods In this retrospective study all consecutive patients who presented between August 2008 and August 2019 were screened for the presence of a macular hole and only iFTMHs were included. The primary outcome measure was the spontaneous closure of the iFTMH.

Results Of 1256 eyes with macular holes, 338 fulfilled the inclusion criteria. Spontaneous closure of the iFTMH was detected in 31 eyes (9.2%) with a median time of 44 days after diagnosis. Eyes exhibiting spontaneous closure demonstrated a higher baseline best-corrected visual-acuity (BCVA) and smaller iFTMH diameter ($p < 0.0001$ and $p < 0.0001$, respectively). The mean BCVA improved from 0.4 logMAR (SD ± 0.21) to 0.29 logMAR (SD ± 0.20) after spontaneous closure ($p = 0.031$). The iFTMH diameter was positively correlated with the time to spontaneous closure (Pearson- $r = 0.37$, $p = 0.0377$). Spontaneously closed iFTMHs reopened in 16% ($n = 5$) of cases, with a median of 136 days after closure. A logistic regression model showed the hole diameter was associated with spontaneous closure (odds-Ratio 0.97, 95%CI [0.96, 0.98]). The Kaplan–Meier-Curve revealed that approximately 25% of small-iFTMH ($n = 124$) and 55% of iFTMH with a diameter $< 150\mu\text{m}$ ($n = 48$) closed spontaneously within two months.

Conclusion The established gold-standard for the treatment of iFTMHs is macular surgery. However, the potential for spontaneous closure of small iFTMHs must be acknowledged. Therefore, if surgical treatment is delayed in individual cases, close observation is recommended.

Keywords Macular Hole · Full Thickness Macular Hole · Spontaneous Closure · Time Course · Re-opening · Watch and Wait

Key messages

What is known:

- Spontaneous closure of idiopathic full-thickness macular holes (iFTMH) is a known phenomenon, however, additional information is required to understand the time course and likelihood of its occurrence.

What is new:

- Spontaneous closure of iFTMHs was detected in 9.2% of eyes and depends on the diameter of the hole.
- Approximately 25% of small iFTMHs and 55% of iFTMHs with diameters $< 150\mu\text{m}$ close spontaneously within two months of diagnosis.
- In case of spontaneous closure of iFTMHs, a reopening of the hole is possible, emphasizing the importance of close follow-up.

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Introduction

An idiopathic full-thickness macular hole (iFTMH) is a vitreomacular interface disease with an opening of all neurosensory retinal layers in the fovea, leading to vision loss, metamorphopsia and central scotoma. It is more frequently observed in women over the age of 65, with an incidence of about eight eyes per 100,000 per annum [1]. Following the report of the first surgical closure of iFTMHs by Kelly and Wendell, advanced vitreoretinal surgical techniques contributed to successful postoperative restoration of the foveal microstructure with improvement of the vision [2–7]. There have been also efforts to achieve closure of iFTMH by intravitreal pharmacotherapy, which resulted in a favorable outcome in selected cases [8]. Currently, the first-line therapy for the iFTMH is macular surgery.

Although the macular surgery is a safe and effective, spontaneous closure of iFTMHs has been reported repeatedly over the years [9–13]. Before the introduction of Optical Coherence Tomography (OCT), spontaneous closure of iFTMHs was described in several studies, ranging from 0% to 15.8% [14–16]. However, given the difficulty of diagnosing small iFTMHs by funduscopy, these studies are subject to possible bias. To our knowledge, few studies have investigated the spontaneous closure of iFTMH using OCT imaging [17–19].

While the aforementioned reports focused on the rates of spontaneous closure, the dynamics of this phenomenon are also critical, as delayed surgery is associated with poor prognosis [20, 21]. Therefore, the aim of this study was to investigate the factors related to the spontaneous closure and the time course of this phenomenon in particular.

Methods

We retrospectively reviewed the electronic medical charts of all patients presenting between August 2008 and August 2019 at the Department of Ophthalmology of the University of Tuebingen and included 1256 eyes diagnosed with an iFTMH. All patients underwent complete ophthalmologic examination, including best-corrected visual acuity (BCVA), slit-lamp biomicroscopy and dilated funduscopic evaluation. Spectral domain OCT (Heidelberg Engineering GmbH, Heidelberg, Germany) was performed at the first presentation and in all follow-up examinations. Patients received a volume scan (25 cross sections with a distance of 61 μm) and six or 12 radial scans. The primary outcome measure was a spontaneous closure of the iFTMH detected on OCT imaging. Inclusion criteria were: 1- Available SD-OCT at the first presentation and follow-up examinations; 2- SD-OCT examination one day before

the scheduled macular surgery. Exclusion criteria were: 1- Previous intravitreal pharmacotherapy; 2- Ocular diseases that could interfere with morphology of the macula or the visual prognosis; 3- Ocular trauma; 4- Previous vitreoretinal surgery, laser photocoagulation or cryosurgery; 5- Myopia of less than minus six diopters (< -6 Diopters); 6- Missed OCT-examination or poor image quality; 7- Secondary full-thickness macular holes. The diagnosis of an iFTMH was based on the OCT imaging and the classification by the International Vitreomacular Traction Study (IVTS) Group was used for grading [22]. The iFTMH diameter was determined by measuring the smallest distance at the mid-retina on the selected OCT scan that captured the widest cross-sectional image of the macular hole [22]. To ensure the reliability of the measurements, 30 eyes were randomly selected, and the diameter of the iFTMH was measured by a second ophthalmologist without revealing the value of the first measurement, resulting in an excellent intraclass correlation of 0.95. The presence of vitreomacular traction and epiretinal membrane was documented. Patients were informed about the natural course and therapy options, including close observation in case of a small iFTMH and good baseline BCVA, intravitreal pharmacotherapy in selected cases, and vitrectomy with macular surgery. The surgery was scheduled as soon as possible, and the OCT examination was repeated on the day before the surgery. For the creation of Kaplan–Meier curves all available data were considered. In the absence of spontaneous closure, the last OCT scan with an iFTMH was noted as the date of censoring.

The iFTMHs were graded as proposed by the International Vitreomacular Traction Study Group (IVTS) in small ($\leq 250 \mu\text{m}$), medium (251–400 μm) and large ($> 400 \mu\text{m}$) iFTMHs and depending on the presence/absence of vitreofoveal traction [22]. Visual acuity was analyzed using logMAR. Statistical analysis was performed using R and Prism 6, GraphPad. The D'Agostino and Pearson omnibus normality test, Fisher's test, Chi-square test with Yates' correction and Mann–Whitney U test were used and statistical significance was assumed for $p < 0.05$. This study was performed according to the principles of the Declaration of Helsinki and it was approved by the Ethics Committee of the University of Tuebingen (Project Number 215/2020BO2).

Results

Of the total 1256 eyes with iFTMH, 338 fulfilled the inclusion criteria. A total of 918 eyes were excluded (549 eyes with previous intraocular surgery or associated macular diseases, 360 eyes without OCT examination and nine eyes with low-quality of the OCTs). The study cohort comprised 338 eyes

of 324 patients (199 women) with a mean age of 68.9 years (range 40–90 years). Bilateral involvement was observed in 14 patients (4.1%) at the first visit or during the follow-up period. The time interval between the diagnosis and surgery was in median 34 days (range 4–618). Of the patients without spontaneous closure ($n=307$), 279 (90.9%) agreed to have surgery. A total of 28 patients (28 eyes, 9.1%) refused surgery. The median follow-up time of these patients was 149 days (range 16–1849). In the spontaneous closure group, two out of 31 patients refused surgery. No significant difference was found between the two groups regarding surgery refusal ($p=1$). Table 1 summarizes the baseline characteristics of the study population.

Spontaneous closure of the iFTMH was detected in 31 eyes (9.2%) of 30 patients with a median time of 44 days

(range 5–1013) after diagnosing the iFTMH. One patient showed spontaneous closure in both eyes. No significant differences were observed in terms of diameter or time to spontaneous closure between patients with and without vitreomacular traction ($p=0.40$ and $p=0.55$, respectively). Eyes with spontaneous closure had a higher baseline BCVA and smaller iFTMH diameter ($p<0.0001$ and $p<0.0001$, respectively), and there was no statistically significant difference in age, gender, lens status, frequency of vitreofoveal traction or the presence of an epiretinal membrane ($p=0.13$, $p=0.25$, $p=1$, $p=0.10$ and $p=0.40$, respectively). The mean BCVA improved significantly from 0.4 logMAR (SD ± 0.21) to 0.29 logMAR (SD ± 0.20) after spontaneous closure ($p=0.031$). In eyes with spontaneous closure, the diameter of the iFTMH

Table 1 Baseline characteristics of the study population

	No Spontaneous Closure ($n=307$)	Spontaneous Closure ($n=31$)	
Age, mean	69,11 (SD 7,98) (range, 40–89 years)	66,77 (SD 9,24) (range, 54–90 years)	$p=0.13^1$
Sex	184 female (60%) 123 male (40%)	15 female (48%) 16 male (52%)	$p=0.25^2$
Lens			
Phakic	223 (73%)	23 (74%)	$p=1^2$
Pseudophakic	84 (27%)	8 (26%)	
BCVA Baseline (mean)	0.68 (SD 0.27)	0.40 (SD 0.21)	$p<0.0001^3$
Gass Classification			
2	94 (31%)	31 (100%)	
3	70 (23%)	-	
4	142 (46%)	-	
IVTS Classification*			
Small without VMT	62 (20%)	17 (55%)	
Small with VMT	31 (10%)	14 (45%)	
Medium without VMT	75 (24%)	-	
Medium with VMT	39 (13%)	-	
Large without VMT	78 (25%)	-	
Large with VMT	22 (7%)	-	
Vitreomacular Traction			
No	215 (70%)	17 (55%)	$p=0.10^2$
Yes	92 (30%)	14 (45%)	
Epiretinal Membrane			
No	224 (73%)	20 (65%)	$p=0.40^2$
Yes	83 (27%)	11 (35%)	
Mean Diameter (μm)	345,6 (SD 161,6)	98,9 (SD 58,32)	$p<0,0001^3$
Median Time to Spontaneous Closure (days)		44 (range, 5–1013)	

BCVA: Best-corrected visual acuity

VMT: Vitreo-macular traction

SD: Standard deviation

¹ Unpaired t-test (with D'Agostino & Pearson Omnibus normality test)

² Fisher's exact test

³ Wilcoxon-Mann-Whitney-Test

* IVTS Classification: Small $\leq 250 \mu\text{m}$, Medium $> 250 \mu\text{m}$ and $\leq 400 \mu\text{m}$, Large $> 400 \mu\text{m}$

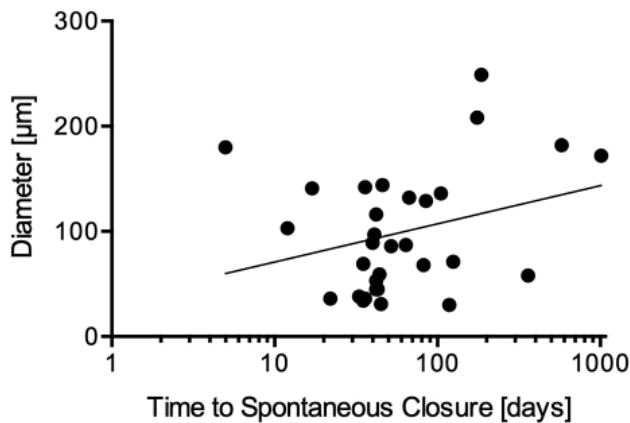


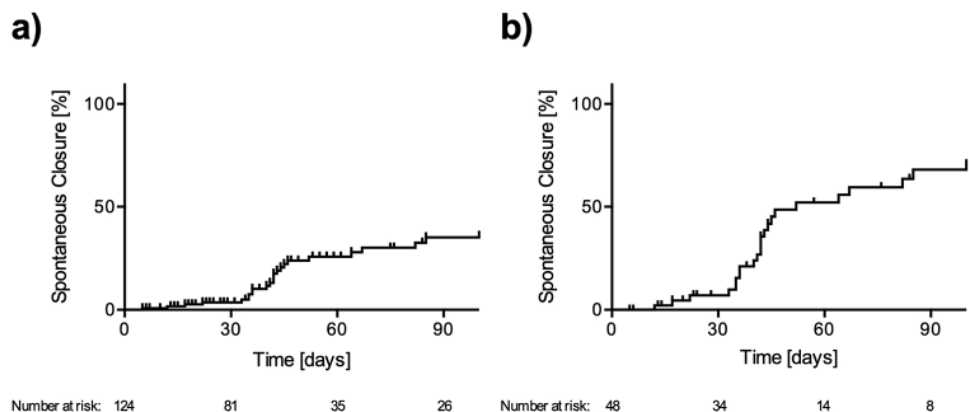
Fig. 1 Semi-logarithmic regression of idiopathic full-thickness macular hole (iFTMH) diameter and the time to spontaneous closure ($n=31$). A smaller iFTMH diameter was significantly correlated with a shorter time to spontaneous closure (Pearson $r=0.37$, $p=0.0377$)

was positively correlated with the time to spontaneous closure (Pearson $r=0.37$, $p=0.0377$) (Fig. 1).

In the logistic regression analysis of age, baseline BCVA, lens status, status of vitreofoveal traction and iFTMH diameter, only the diameter $[\mu\text{m}]$ was found to be significantly associated with spontaneous closure (odds Ratio 0.97, 95%CI [0.96, 0.98]). The mean diameter of the spontaneously closed iFTMH was $98.9 \mu\text{m}$ (range $30\text{--}249 \mu\text{m}$), corresponding to a small iFTMH. The median follow-up after spontaneous closure (available for 23 patients, 74.1%) was 406 days (range 21 to 4161 days). A re-opening of the spontaneously closed iFTMH was found in five eyes (16.1%) after a median of 136 days after closure (range 23 to 708 days).

Since spontaneous closure was observed in eyes with small iFTMHs ($n=124$), we plotted this data on a Kaplan–Meier curve and found that approximately 25% of the iFTMHs closed spontaneously within two months. For a diameter of $<150 \mu\text{m}$ ($n=48$), the frequency of the spontaneous closure increased to 55% of eyes within that time period (Fig. 2).

Fig. 2 Kaplan–Meier-Plot of spontaneous closure. Upward blips represent censored patients. **a** Approximately 25% of idiopathic full-thickness macular holes (iFTMH) with a diameter $\leq 250 \mu\text{m}$ ($n=124$) close spontaneously within two months of diagnosis. **b** 55% of iFTMHs with a diameter $\leq 149 \mu\text{m}$ ($n=48$) close spontaneously within two months of diagnosis



Discussion

The study included 338 eyes with iFTMHs and revealed a spontaneous closure rate of 9.2% at a median of 44 days after the diagnosis. All eyes with spontaneous improvement had small iFTMHs.

Previous retrospective studies using OCT imaging for iFTMH diagnosis reported spontaneous closure in 2.7–3.5% of eyes, while the mean time to spontaneous closure were 2, 2.5, and 5 months [17–19]. The time to closure was similar in our large cohort, however, we found a higher rate of spontaneous closure (9.2%). This discrepancy may be explained by the different study populations. In our study, eyes with spontaneous closure had an average hole diameter of $98.9 \mu\text{m}$, which was smaller compared to $201 \mu\text{m}$, $195 \mu\text{m}$ and $162 \mu\text{m}$ found in previous studies. This might suggest that patients with smaller iFTMH are underrepresented in the other studies, leading to a lower spontaneous closure rate.

One of the prospective studies investigating the effect of ocriplasmin in eyes with vitreomacular traction or iFTMH found in the control group a spontaneous closure rate of 15.4% (4/26 eyes with iFTMH) at month three without re-opening in the 24-month follow-up period [8, 23, 24].

In our study population, spontaneous closure was found only in eyes with small iFTMHs, whereas in the mentioned retrospective studies, few eyes had diameters greater than $250 \mu\text{m}$ [17–19]. Smaller iFTMHs have been reported to have a higher likelihood of spontaneous closure. Our study found a significant correlation between hole diameter and spontaneous closure.

There are also reports regarding the spontaneous re-opening between three months and three years after achieving complete iFTMH closure with or without surgical intervention [10, 25–27]. In our study population, we found re-opening of spontaneously closed iFTMH in five patients with a median of 4 months after closure. Considering the relatively short time span until reopening,

the continuation of the regular follow-up examinations is important. In our clinic, patients were advised to have follow-up examinations at 2-week intervals for 6 weeks after the initial diagnosis. Subsequently, ophthalmological examinations were performed alternately with local ophthalmologists at four-week intervals, provided an OCT examination was available. As all patients in our study had full health insurance, it is unlikely that any missed follow-up examinations were due to monetary reasons. Although we cannot be certain, we assume that patients were referred if any morphological or functional worsening was noticed by the local ophthalmologists. All patients with a re-opening after spontaneous closure underwent macular surgery and showed closure of the iFTMH. Due to the small number of observed re-opened iFTMHs, further statistical analysis of OCT features was not feasible. In the aforementioned retrospective studies and the prospective OASIS study, only one re-opening was described which might be due to the lower number of observed spontaneous closed iFTMHs compared to our study [17–19, 23, 25, 28].

The exact mechanism of spontaneous closure of iFTMH remains unknown. One explanation is that the release of vitreous traction leads to decreased vertical forces and to a flattening and convergence of the hole edges [29]. However, since the proportion of eyes with and without vitreofoveal traction was comparable in both groups (30% in the no spontaneous closure group, and 45% in the spontaneous closure group, $p=0.103$), other mechanisms should also be considered. Furthermore, closure of the iFTMH with persistent vitreofoveal traction is also reported [18]. Consequently, we would consider the release of vitreofoveal traction favorable for spontaneous closure, although this cannot be generalized for all cases with vitreofoveal traction.

Interestingly, in case reports of secondary full-thickness macular holes associated with cystoid macular edema in uveitis, ocular trauma, post-laser inflammation, or Irvine-Gass syndrome, the resolution of the intraretinal pseudocysts is thought to have contributed to spontaneous closure [10, 26, 30–36].

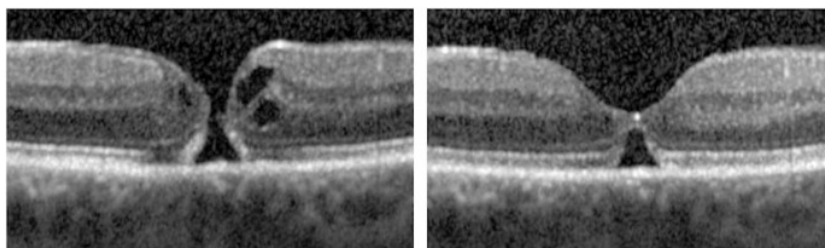
The formation of a bridge-like structure at the edges of the hole is thought to be a reparative reaction of the Müller cells preceding the spontaneous closure [37–39]. In line with these reports, many eyes with spontaneous closure in our study presented with a bridging phenomenon in the OCT (Fig. 3).

So far, limited information is known about the time course of spontaneous closure of the small iFTMHs. Based on the data presented, approximately 25% of small iFTMHs (diameter $\leq 250 \mu\text{m}$) and around 50% of iFTMHs with diameters $< 150 \mu\text{m}$ can close spontaneously within two months of diagnosis. Therefore, in patients with small iFTMHs and relatively good vision a „watchful waiting“ approach with short follow-up regime may be offered to some patients after careful considerations of all circumstances. However, a recent meta-analysis estimated a minor vision loss of 0.008 logMAR per month of additional waiting for surgery [20]. As this study included iFTMHs of all sizes, and small iFTMHs have a higher surgical success rate, extrapolating the degree of vision loss for small iFTMHs only is difficult [20, 21].

One of the main limitations of this study is its retrospective study design. However, we believe that our analysis is rather underestimating spontaneous closure rates because patients with spontaneous BCVA improvement may not seek ophthalmological examination in the first place or are more likely to miss follow-up appointments. Moreover, the time of the iFTMH closure is likely overestimated, as spontaneous closure was diagnosed on the day of the OCT examination and not at the time of subjective BCVA improvement. However, it is notable that the time of diagnosis based on the OCT examination is not the time at which the iFTMH actually develops. An alternative to our approach is using the onset of symptoms as the time of diagnosis. Nevertheless, we have decided against this, as not all patients are able to state the onset of symptoms precisely enough (e.g. if the healthy partner eye is dominant). Therefore, caution should be applied when generalizing these results.

In summary, this study revealed spontaneous closure of small iFTMHs in a relatively high percentage of patients within two months of diagnosis in our cohort. Considering that the established standard therapy for iFTMHs is a surgical approach, this information could be relevant to clinical practice and future studies. While our data cannot be used to predict the course of an individual patient's disease with high accuracy, future investigations are required to validate the conclusions drawn from this study and to help establish validated treatment recommendations for patients with small iFTMHs in the clinical routine.

Fig. 3 Spontaneous closure of an idiopathic full-thickness macular hole with bridging phenomenon in a 57-year-old lady 52 days after diagnosis



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Author contribution Conceptualization & methodology, All; investigation & data curation, J.N., F.G., T.Ö.; writing—original draft preparation, J.N.; writing—review and editing, all; visualization, J.N.; supervision, J.N., F.G.; All authors have read and agreed to the published version of the manuscript.

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Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki and it was approved by the Ethics Committee of the University of Tuebingen (Project Number 215/2020BO2).

Informed consent Patient consent was waived due to the retrospective nature of the study and because only anonymous clinical data was analyzed.

Competing interests The authors declare no conflict of interest.

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