
Characteristics and Outcomes of Full-thickness Macular Hole Repair in Patients Receiving Anti-VEGF Injections for Neovascular Age-related Macular Degeneration

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■ Background

Full-thickness macular hole (FTMH) was first described by Knapp¹ in the late 1800s. Recent classification has described FTMH as an anatomic defect in the fovea featuring interruption of all neural retinal layers from the internal limiting membrane to the retinal pigment epithelium (RPE).² FTMH most commonly occurs in the seventh decade of life and there is a significant female predominance. The vast majority of FTMH occur as an age-related idiopathic condition unrelated to other ocular comorbidities. In most of these cases, FTMH develops in conjunction with vitreomacular traction (VMT). When FTMH occurs in the setting of concurrent macular disease, the mechanism may involve VMT, pathologic characteristics of the retina other than VMT, or a combination of factors.

Review of the Literature Regarding FTMH in Various Maculopathies

Adult-onset Foveomacular Vitelliform Dystrophy (AOFVD)

AOFVD is a genetic macular dystrophy characterized by bilateral blurred vision, metamorphopsia, and visual impairment secondary to a grayish-yellow lesion located in the fovea. Patients typically present in their 30s to 50s. Optical coherence tomography (OCT) locates the vitelliform lesion to the retinal pigment epithelium (RPE) layer or the space between the RPE and photoreceptor layer. FTMH is a rare complication of AOFVD

but has been observed in multiple reports.^{3,4} Two mechanistic theories exist to explain the formation of FTMH in AOFVD: (1) FTMH may develop in the vitelliruptive stage when the lesion breaks up, and as the retina/RPE becomes atrophic, a macular hole becomes apparent or (2) Lowered RPE function results in fluid accumulation in the subretinal space that leads to weakening attachments of the sensory retina to the RPE and ultimately causes a macular hole.⁵

Best Disease Best disease is an autosomal dominant disease caused by mutations in the bestrophin (VMD2) gene.⁶ It has variable expression secondary to diminished penetrance and typically presents in adolescence or early adulthood. Visual acuity is typically better than expected given the striking appearance of the macular lesion. Macular hole associated with best disease has been observed in the literature.^{7,8} Similar to AOFVD, rupture of the cyst in the vitelliruptive phase and atrophic changes in the RPE layer during the late stages of the disease have been proposed as the etiology of FTMH in these patients.

Stargardt Disease Stargardt disease is an autosomal recessive macular dystrophy characterized by mutations to the *ABCA4* gene.⁹ Visual deterioration in these patients is highly variable and yellowish-white pisciform flecks are the clinical hallmark of this disease. To date, one report of FTMH associated with Stargardt disease has been published.¹⁰ In this report, the FTMH occurred secondary to VMT over an area of preexisting foveal geographic atrophy. The authors achieved anatomical success following pars plana vitrectomy (PPV) with internal limiting membrane and epiretinal membrane peeling. However, the patient's visual acuity remained stable because of underlying chorioretinal atrophy.

Type II Idiopathic Macular Telangiectasia Macular telangiectasia is a degenerative macular disorder first described by Gass and Oyakawa¹¹ in 1982. The type II version of this disease is typically bilateral and characterized clinically by retinal crystalline deposits and abnormal vascular findings such as ectatic capillaries, dilated vessels and right-angled vessels that appear to dive into the deeper layers of the retina. Early OCT findings include temporal extension of the foveal depression or disruption of the ellipsoid zone temporal to the fovea.¹² Late OCT findings include retinal cavitations and temporal atrophy with draping of the internal limiting membrane. In addition to individual cases reports, two cases series have been published reporting the association of FTMH with Type II idiopathic macular telangiectasia.^{13,14} The majority of these cases demonstrated typical sized FTMHs but pathognomonic macular telangiectasia type II changes were noted adjacent to the FTMH including temporal atrophy and retinal cavitations. In many cases, the

authors noted development of the FTMH without the presence of preexisting VMT. Karth et al¹⁴ demonstrated that surgical treatment in this patient population may be less successful when compared to idiopathic FTMH because of the absence of abnormalities of the vitreomacular interface and preexisting retinal atrophic changes.

Central Serous Retinopathy (CSR) CSR is a common maculopathy thought to occur secondary to hyperpermeable choroidal capillaries and RPE dysfunction resulting in a localized serous retinal detachment. FTMH associated with CSR has only been reported in the literature once to date.¹⁵ In this case, the hole was successfully closed with PPV and membrane peeling (MP). However, the patient returned with active CSR seven months following FTMH repair.

Pathologic Myopia Pathologic myopia is defined as degenerative retinal changes associated with globe elongation and refractive error of at least -6 diopters or an axial length of ≥ 26.5 mm. These patients are more susceptible to FTMH formation because of axial elongation of the eye resulting in stretching and thinning of the choroid and RPE layers.¹⁶ These patients may develop total retinal detachment following FTMH formation and often require multiple surgeries to achieve anatomical success. A recent meta-analysis by Gao et al¹⁷ reported a primary surgical closure rate of 58% with PPV and internal limiting membrane peeling in this group of patients. The authors found that severe vision loss was common, even with anatomically successful FTMH repair.

Diabetic Macular Edema (DME) and Proliferative Diabetic Retinopathy (PDR) Eyes with DME may develop FTMH because of intraretinal exudation combined with increased vitreomacular attachments and traction.¹⁸ In diabetic eye disease, iatrogenic FTMH formation is also possible following PPV with removal of fibrovascular tissue in PDR, likely as a result of direct tractional forces exerted during peeling.

■ Current Study

Purpose

FTMH formation with concomitant macular disease or in association with anti-vascular endothelial growth factor (VEGF) treatment has been infrequently reported in the literature. In this report, we report the largest case series to date of patients who developed FTMH, whereas receiving anti-VEGF treatment for neovascular age-related macular degeneration (nAMD).

Methods

This study is a retrospective, noncomparative case series. Salus Institutional Review Board (Austin, TX) approval was obtained for this retrospective series, which adheres to the tenets of the Declaration of Helsinki.

A search of the diagnostic and procedure database at one participating retina practice (Vitreoretinal Surgery, PA Minneapolis, MN) identified 10 patients being treated with anti-VEGF therapy for nAMD who subsequently developed FTMH from 2012 to 2017. Exclusion criteria included choroidal neovascular membrane (CNVM) of any cause except nAMD, and previous FTMH in the affected eye. All of the injections were performed under standard sterile conditions. All patients underwent pars plana vitrectomy with membrane peel for the FTMH.

At the start of anti-VEGF therapy, all patients underwent best-corrected visual acuity (BCVA) measurement, ophthalmic examination including slit-lamp biomicroscopy, and time-domain or spectral-domain OCT. Fluorescein angiography (FA) was performed to confirm diagnosis of nAMD and to exclude other causes of CNVM. At each follow up visit, complete eye examination was performed, including BCVA measurement, funduscopy, and OCT.

Results

Individual case data is presented in Table 1. Figure 1 represents images from Patient no. 8. The mean age of patients in this study was 75.3 years and 7 (70%) patients were female. Preexisting vitreomacular adhesion (VMA) without traction was present in 9 (90%) cases and absent in 1 (10%) case as documented on OCT. All patients had received at least three intravitreal injections of bevacizumab, ranibizumab, or aflibercept before FTMH development. The mean number of injections before development of the FTMH was 19.1 (range, 3 to 39). The mean number of days following last injection before FTMH diagnosis was 51.5 days (range, 28 to 164). Following PPV, the FTMH was closed in all cases (a 100% primary closure rate). SF6 gas was used in 5 (50%) cases and C3F8 gas was used in 5 (50%) cases. Preoperatively, the CNVM involved a subfoveal pigment epithelial detachment (PED) in 9 (90%) cases and was unable to be characterized in 1 (10%) case before a large submacular hemorrhage. Nine (90%) patients continued to receive anti-VEGF treatment following PPV for FTMH repair. The mean number of injections following PPV in these patients was 11.6 (range, 0 to 42). The mean injection interval (mean interval of last 3 injections before PPV versus mean interval of last 3 injections during study time period) decreased from an average of 83.9 days to 51.5 days following FTMH repair. However, this result was not statically significant ($P > 0.7$).

Table 1. Summary of Patients Receiving Anti-VEGF Injections for nAMD Who Subsequently Developed FTMH

Patient	Age	Sex	Eye	VA at Presentation of nAMD	Preop VA	Postop VA	FTMH Closed Postop?	No. Injections Before PPV	No. Injections After PPV	No. days after Injection FTMH Identified	PED?	Preexisting VMT?
1	66	F	OD	CF	20/200	20/400	Yes	3	4	35	Unknown	Yes
2	78	F	OD	20/20	20/40	20/20	Yes	5	3	164	Subfoveal	No
3	83	F	OD	20/30	20/400	20/150	Yes	39	29	35	Subfoveal	Yes
4	76	M	OS	20/40	20/100	20/50	Yes	30	42	35	Subfoveal	Yes
5	83	F	OD	20/50	20/200	20/200	Yes	15	10	28	Subfoveal	Yes
6	70	F	OD	20/50	20/150	20/400	Yes	38	10	56	Subfoveal	Yes
7	71	M	OS	20/50	20/100	20/40	Yes	9	0	182	Subfoveal	Yes
8	69	M	OS	20/25	20/320	20/80	Yes	20	12	49	Subfoveal	Yes
9	77	F	OD	20/30	20/400	20/200	Yes	22	3	63	Subfoveal	Yes
10	80	F	OD	20/30	20/80	20/80	Yes	10	3	28	Subfoveal	Yes

All patients underwent PPV with MP for treatment of FTMH.

FTMH indicates full-thickness macular hole; nAMD, neovascular age-related macular degeneration; PED, pigment epithelial detachment; PPV, pars plana vitrectomy; VA, visual acuity; VEGF, vascular endothelial growth factor; VMT, vitreomacular traction.

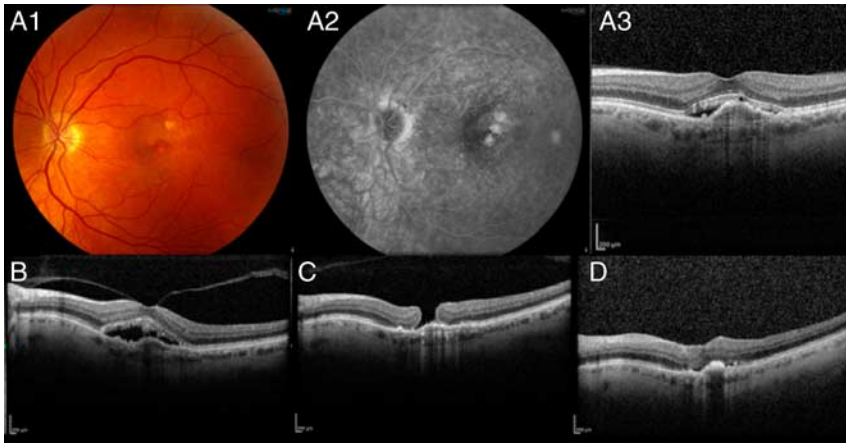



Figure 1. A1, A 69-year-old male who presented with nAMD OS. Visual acuity at the time of presentation was 20/25. Clinically, the patient exhibited a pigment epithelial detachment, drusen, RPE changes, and subretinal fluid. A2, Fluorescein angiography revealed transmission defects secondary to RPE changes, pooling secondary to a PED, and leakage consistent with a CNVM. A3, OCT at the time of presentation exhibited RPE elevation consistent with a PED and subretinal fluid. B, Following 19 anti-VEGF injections, the patient's visual acuity was 20/30 and the OCT exhibited persistent subretinal fluid with evidence of mild VMT. C, When the patient returned for anti-VEGF treatment #20, his visual acuity had dropped to 20/320 and OCT showed a PED with a FTMH. D, The patient underwent PPV with internal limiting membrane peeling and a closed FTMH hole was noted on OCT testing at postoperative week #2. The patient's visual acuity at postoperative week #2 was 20/250. One year following FTMH repair, the patient continued to receive anti-VEGF therapy and his visual acuity was 20/80. 

Following FTMH repair, 6 (60%) patients had improvement in their BCVA, in 3 (30%) patients the BCVA was unchanged, and 1 (10%) patient had worsening of BCVA when compared to BCVA at time of FTMH diagnosis. In 7 (70%) patients, the best corrected visual acuity (BCVA) following FTMH repair was worse than their BCVA at the time of presentation with nAMD. All patients were followed for a minimum of 6 months following FTMH repair.

Discussion

nAMD is the leading cause of irreversible vision loss in people older than 50 years of age in the developed world.¹⁹ Vision loss in nAMD occurs secondary to development of CNVM and VEGF is the primary pathophysiologic factor involved. Therefore, over the past 2 decades, anti-VEGF treatment has become the standard of care in nAMD to prevent severe vision loss and in some cases even improve vision.²⁰ Today, 3 anti-VEGF medications dominate the treatment landscape and have similar side effect and adverse event profiles. In large clinical trials, adverse events following intravitreal injection of anti-VEGF medications are rare (<1%) and include endophthalmitis, retinal pigment

epithelium (RPE) rip, retinal tear, rhegmatogenous retinal detachment, traumatic cataract, vitreous hemorrhage, and intraocular inflammation.²¹

FTMH formation following anti-VEGF treatment for AMD has been reported in a number of case reports and small case series.²²⁻³⁰ Authors of these reports have discussed multiple mechanisms of FTMH development, and although the characteristics of these FTMH may vary based on the underlying maculopathy, these FTMH generally differ from idiopathic FTMH in having a poorer visual prognosis. The anatomic success rate with vitrectomy may also be lower secondary to the macular comorbidity.

VMA and VMT have been implicated as risk factors for the development of nAMD, whereas presence of a posterior vitreous detachment has been shown to be protective against the development of neovascularization.^{31,32} Geck et al³³ reported that 24% of patients initiating anti-VEGF injections for nAMD developed a PVD over an average of 11.1 weeks. This was more prevalent with increasing age. Therefore, anti-VEGF therapy in patients without preexisting PVD may increase the risk of FTMH early in the treatment course by inducing vitreoretinal tractional forces. Other authors have theorized that vitreous incarceration at the site of needle entry during an intravitreal injection may increase VMT, possibly leading to FTMH formation.³⁴

Some prior reports have focused on the presence of a subfoveal PED in many cases of FTMH associated with nAMD.^{28,35} In these cases, the neurosensory retina including the photoreceptor layer overlying the PED is stretched out of its normal anatomical configuration. The pigment epithelial layer and outer retina at the fovea are diseased in the setting of center-involving AMD, possibly compromising the pump function and adherence of the outer retina to the pigment epithelium. Use of an anti-VEGF agent may then alter the height and size of the PED inducing further stressors on the fovea. This combination of factors can lead to the development of a FTMH. Oshima et al²⁹ reported development of a FTMH following a RPE rip, which may share a similar mechanism with even more rapid contraction of the underlying tissue.

In our case series, FTMH most commonly developed in patients with preexisting VMA and a subfoveal PED. As aforementioned, the combination of VMT forces and the presence of a PED, which alters the fovea anatomy, may be what most commonly predisposed our cohort to FTMH development. Although not statistically significant, it should be noted that in our cohort the average injection interval decreased following PPV. As discussed in previous studies, this is likely secondary to increased vitreous clearance of anti-VEGF medications.³⁶

Although most of these patients continue to need anti-VEGF therapy and do not return to their BCVA at the time of initial presentation with nAMD (before FTMH formation), our cohort exhibited a 100% closure rate of the FTMH with PPV and 60% of patients had BCVA gain from the

time of diagnosis with FTMH. Patients with preexisting geographic atrophy in the fovea and underlying the FTMH may be less likely to have BCVA gains following surgical repair. Careful evaluation of the patient's OCT may give further prognostic value. Ultimately it is important to counsel the patient and family that FTMH repair in the setting of nAMD is unlikely to yield visual acuity gains comparable to those of the idiopathic FTMH cohort but that surgical repair is still often visually worthwhile.

The authors declare that they have no conflicts of interest to disclose.

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