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Full-Thickness Macular Hole Formation Following Intravitreal Aflibercept Therapy for Neovascular Age-Related Macular Degeneration

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ABSTRACT: *Age-related macular degeneration (AMD) is the leading cause of irreversible central vision loss in the elderly population, with choroidal neovascularization (CNV) representing the hallmark feature of its neovascular form. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy has become the standard treatment for neovascular AMD, with aflibercept demonstrating excellent efficacy and safety. However, rare complications may occur. We describe a 68-year-old woman diagnosed with neovascular AMD associated with subfoveal CNV, neurosensory retinal detachment, drusenoid pigment epithelial detachments, and incomplete posterior vitreous detachment. Following a loading regimen of three intravitreal aflibercept injections administered at four-week intervals, the patient developed a sudden decrease in visual acuity and central scotoma. Optical coherence tomography revealed a large full-thickness macular hole with widely separated retinal edges and intraretinal cystic changes. Combined phacoemulsification and pars plana vitrectomy using the inverted internal limiting membrane flap technique with 20% sulfur hexafluoride gas tamponade was performed. Successful anatomical closure of the macular hole was achieved, with visual acuity improving from 0.03 to 0.2. During 12 months of follow-up, the choroidal neovascular membrane remained inactive without the need for additional anti-VEGF therapy, and both anatomical and functional outcomes remained stable. The development of full-thickness macular hole following anti-VEGF treatment is an uncommon event that may be related to vitreomacular interface alterations, contraction of the neovascular membrane, and structural changes associated with pigment epithelial detachment remodeling. Careful OCT monitoring before and during treatment may facilitate early recognition of this rare complication and allow timely surgical intervention with favorable visual and anatomical results.*

KEYWORDS: *Age-related macular degeneration, Choroidal neovascularization, Aflibercept, Anti-VEGF, Full-thickness macular hole, Pars plana vitrectomy, Optical coherence tomography.*

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I. INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of irreversible central vision loss among elderly individuals worldwide and its prevalence increases with age, ranging from 0.2% to 13% [1]. The disease is characterized by progressive degeneration of the macula, resulting in impairment of central visual function and a substantial reduction in quality of life. AMD is broadly classified into non-neovascular (dry) and neovascular (wet) forms. Although neovascular AMD (nAMD) accounts for a minority of AMD cases, it is responsible for the majority of cases of severe visual loss [2].

The hallmark of nAMD is the development of choroidal neovascularization (CNV), characterized by the growth of abnormal blood vessels originating from the choroid and extending through Bruch's membrane into the subretinal or sub-retinal pigment epithelium (RPE) space. These newly formed vessels are fragile and prone to leakage, hemorrhage, and fibrovascular proliferation, leading to retinal damage, scarring, and progressive vision loss [3]. While AMD is the most common cause of CNV in elderly patients, neovascularization may also occur in a variety of other retinal and chorioretinal disorders, including pathologic myopia, angioid streaks, inflammatory chorioretinopathies such as multifocal choroiditis and punctate inner choroidopathy, central serous chorioretinopathy, traumatic choroidal rupture, X-linked retinoschisis and macular telangiectasia type 2 [4-8]. Despite differences in etiology, VEGF-mediated angiogenesis represents a common pathogenic pathway underlying CNV formation in these conditions.

The advent of intravitreal anti-VEGF therapy has dramatically improved the prognosis of patients with CNV. Aflibercept is a recombinant fusion protein that functions as a soluble decoy receptor with high affinity for VEGF-A, VEGF-B, and placental growth factor (PlGF). By inhibiting these angiogenic factors, aflibercept effectively suppresses neovascular activity, reduces retinal fluid accumulation, and stabilizes or improves visual

acuity. Consequently, it has become one of the most widely used first-line treatments for neovascular AMD and other VEGF-driven retinal diseases [9].

Despite the proven efficacy and safety of intravitreal aflibercept in the management of neovascular AMD, uncommon adverse events have been reported. Full-thickness macular hole formation is a rare complication, potentially resulting from changes at the vitreomacular interface, contraction of neovascular tissue, or rapid anatomical alterations associated with successful anti-VEGF treatment. We report a case of FTMH formation following three consecutive intravitreal aflibercept injections administered for neovascular AMD.

II. CASE REPORT

A 68-year-old woman presented to our clinic complaining of gradually decreasing vision in both eyes. Her best-corrected visual acuity (BCVA) was 0.7 in the right eye (OD) and 0.1 in the left eye (OS). Intraocular pressure was 17 mmHg OD and 16 mmHg OS. Slit-lamp examination of the anterior segment was unremarkable in both eyes. Fundus examination revealed bilateral drusen consistent with AMD. In the left eye, an elevated subretinal lesion involving the macular region was observed. Spectral-domain optical coherence tomography (SD-OCT) of the right eye demonstrated drusen without evidence of exudation, consistent with non-neovascular AMD. In the left eye, OCT revealed neurosensory retinal detachment (NSD), an incomplete posterior vitreous detachment (PVD), and irregularities of the retinal pigment epithelium (RPE)/Bruch's membrane complex with multiple dome-shaped elevations corresponding to drusen and drusenoid pigment epithelial detachments (PEDs). Hyperreflective subfoveal material associated with subretinal fluid was suggestive of an active CNV, confirming the diagnosis of neovascular AMD (Fig. 1).

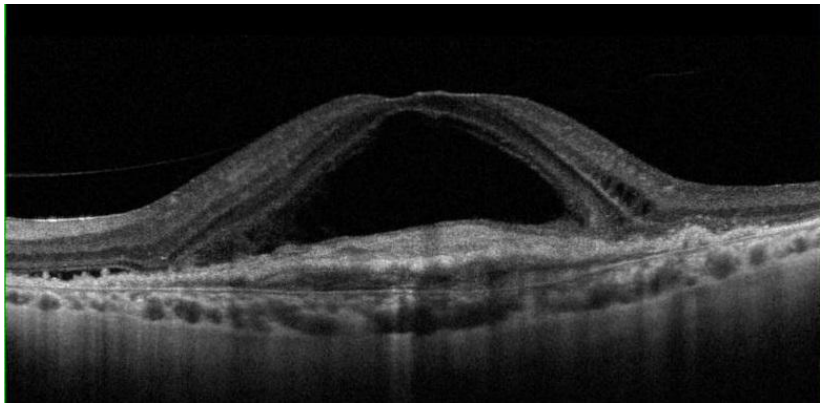

Fig. 1 Baseline OCT of the left eye showing exudative age-related macular degeneration with subretinal fluid and choroidal neovascularization.

In view of the exudative changes, treatment with intravitreal aflibercept was initiated. Following a detailed discussion of the potential benefits and risks of treatment, written informed consent was obtained. The patient underwent three consecutive intravitreal aflibercept injections administered at 4-week intervals. All procedures were performed uneventfully.

One month after the third intravitreal injection, the patient reported the sudden onset of a central scotoma in the left eye. BCVA had deteriorated to 0.03 OS. Repeat SD-OCT demonstrated the development of a large full-thickness macular hole (FTMH) with widely separated retinal edges and intraretinal cystic changes at the margins of the defect. Persistent subfoveal pigment epithelial detachment was also noted (Fig. 2).

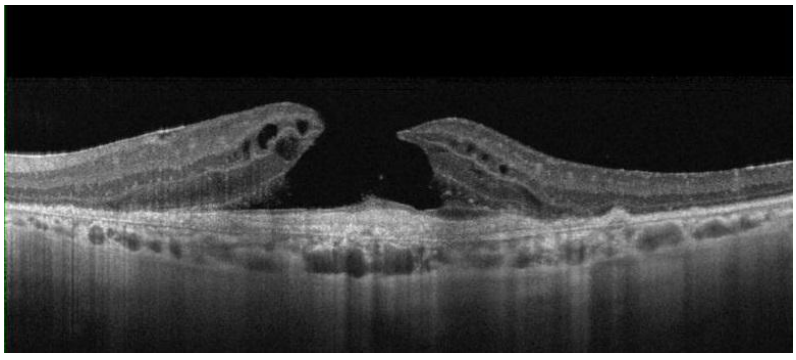

Fig. 2 OCT of the left eye after three consecutive intravitreal aflibercept injections demonstrating a large full-thickness macular hole.

The patient subsequently underwent combined phacoemulsification and pars plana vitrectomy. Vitrectomy was performed using the inverted internal limiting membrane (ILM) flap technique to maximize the likelihood of anatomical closure. Tamponade with 20% sulfur hexafluoride (SF6) gas was performed and no intraoperative anti-VEGF injection was administered.

At the one-month postoperative follow-up visit, SD-OCT confirmed successful anatomical closure of the macular hole (Fig. 3). Although a residual pigment epithelial detachment remained beneath the fovea, the retinal architecture was significantly improved. BCVA improved to 0.2 OS, and the patient reported subjective improvement in central vision.

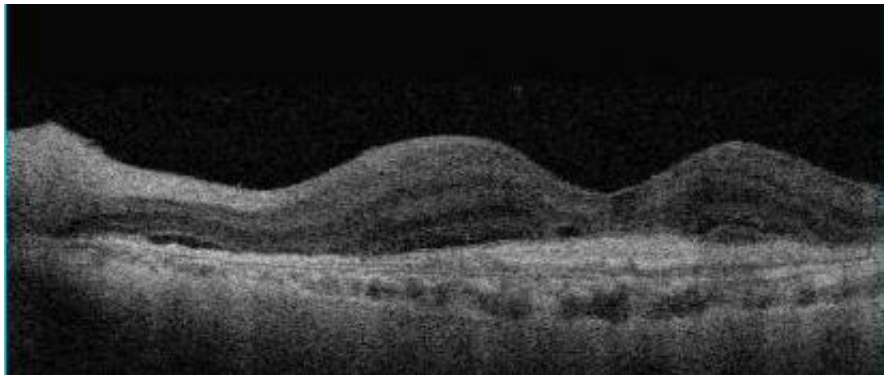

Fig. 3 Postoperative OCT of the left eye demonstrating successful closure of the full-thickness macular hole following pars plana vitrectomy with the inverted internal limiting membrane flap technique.

The patient was subsequently followed for 12 months. Throughout the follow-up period, the choroidal neovascular membrane remained inactive, with no evidence of recurrent intraretinal or subretinal fluid on serial OCT examinations. Given the absence of exudative activity, no additional intravitreal anti-VEGF injections were administered. The anatomical closure of the full-thickness macular hole was maintained, and visual acuity remained stable at 0.2 throughout the follow-up period.

III. DISCUSSION

Full-thickness macular hole is a retinal defect involving all neurosensory retinal layers at the fovea. It most commonly develops as a consequence of vitreomacular traction during posterior vitreous detachment, although secondary causes include high myopia, trauma and inflammatory retinal diseases [10-12].

FTMH formation following intravitreal anti-VEGF therapy is an uncommon complication that has been reported in association with various retinal diseases, including neovascular age-related macular degeneration (nAMD), myopic choroidal neovascularization, and other causes of choroidal neovascularization. Although anti-VEGF agents are highly effective and generally safe, a growing number of case reports have described the development of FTMH after treatment with bevacizumab, ranibizumab, aflibercept and faricimab [13-16].

Several mechanisms have been proposed to explain macular hole formation following anti-VEGF therapy. One of the most widely accepted hypotheses involves alterations of the vitreomacular interface. Intravitreal injections may induce progression of posterior vitreous detachment or generate anteroposterior tractional forces on the fovea [17-19]. In the present case, pre-treatment OCT demonstrated an incomplete posterior vitreous detachment, suggesting the presence of persistent vitreomacular adhesion. The progression of vitreous separation after repeated intravitreal injections may therefore have contributed to increased tractional stress on the fovea, ultimately leading to macular hole formation.

Another potential mechanism is the contraction of the choroidal neovascular membrane following VEGF suppression [20]. Anti-VEGF therapy frequently results in regression and fibrosis of neovascular tissue, which may exert tangential traction on the overlying retina. Such contraction may be particularly relevant in eyes with subfoveal CNV, where mechanical forces generated by the involution of the neovascular complex can directly affect the foveal architecture. In our patient, OCT demonstrated hyperreflective subfoveal material consistent with CNV before treatment, supporting this hypothesis.

Changes in pigment epithelial detachment morphology have also been implicated in the pathogenesis of FTMH. Several authors have suggested that rapid flattening or collapse of PEDs following anti-VEGF therapy may alter the biomechanical relationship between the retinal pigment epithelium and the neurosensory retina, generating tractional forces sufficient to precipitate macular hole formation [19, 21, 22]. In the present case, multiple drusenoid PEDs were present before treatment. Although the PED did not completely resolve, structural modifications induced by anti-VEGF therapy may have contributed to foveal destabilization.

Management of FTMH in eyes with concurrent nAMD remains challenging. Surgeons must address both the mechanical defect and the underlying neovascular pathology. In the present case, pars plana vitrectomy combined with the inverted internal limiting membrane (ILM) flap technique achieved successful anatomical closure of the macular hole. The inverted ILM flap technique has demonstrated high closure rates in large and complex macular holes and was selected because of the large diameter of the defect and the presence of underlying macular pathology [10].

Interestingly, no additional anti-VEGF therapy was required following surgery. During 12 months of follow-up, the choroidal neovascular membrane remained inactive, with no evidence of recurrent intraretinal or subretinal fluid on serial OCT examinations. Anatomical closure of the macular hole was maintained, and visual acuity improved and remained stable throughout the follow-up period. This favorable outcome suggests that successful surgical repair can be achieved without compromising control of the underlying neovascular process.

IV. CONCLUSION

In summary, although intravitreal aflibercept remains a safe and effective treatment for neovascular AMD, clinicians should be aware of the rare possibility of full-thickness macular hole development. The coexistence of vitreomacular interface abnormalities, pigment epithelial detachment, and active subfoveal CNV may predispose susceptible eyes to this complication. Careful structural assessment with OCT before and during treatment may facilitate early recognition and appropriate surgical management, thereby optimizing visual outcomes.

REFERENCES

[1] Smith W, Assink J, Klein R, Mitchell P, Klaver CC, Klein BE, Hofman A, Jensen S, Wang JJ, de Jong PT. Risk factors for age-related macular degeneration: pooled findings from three continents. Ophthalmology. 2001 Apr;108(4):697-704. doi:10.1016/s0161-6420(00)00580-7. PMID: 11297486.

[2] Marchesi N, Capierri M, Pascale A, Barbieri A. Different therapeutic approaches for dry and wet AMD. Int J Mol Sci. 2024 Dec 4;25(23):13053. doi:10.3390/ijms252313053. PMID: 39684764; PMCID: PMC11641571.

[3] Ambati J, Ambati BK, Yoo SH, et al. Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. Surv Ophthalmol. 2003;48:257–93. doi:10.1016/s0039-6257(03)00030-4.

[4] Emin M, Markov G, Zdravkov Y, Oskar A. Choroidal neovascularization in young age associated with moderate myopia [in Bulgarian]. MEDINFO. 2023;23(3):22-25.

[5] Shoumnalieva-Ivanova V, Tanev I, Zdravkov Y, et al. Angioid streaks in Aagenaes syndrome. Int Ophthalmol. 2017;37(4):1065-1068. doi:10.1007/s10792-016-0344-y. PMID: 27614462.

[6] Zhang L, Liu X, Sun L, Zhou X, Ke S, Ding X. Choroidal neovascularisation secondary to X-linked retinoschisis. Br J Ophthalmol. 2024 Oct 22;108(11):1564-1570. doi:10.1136/bjo-2023-324165. PMID: 38811052.

[7] Berger L, Bühler V, Yzer S. Central serous chorioretinopathy – an overview. Klin Monbl Augenheilkd. 2021 Sep;238(9):971-979. doi:10.1055/a-1531-5605. Epub 2021 Aug 20. PMID: 34416788.

[8] Dzhemal N, Markov G, Haykin V, Zdravkov Y, Oskar A. Macular telangiectasia type 2: clinical case report [in Bulgarian]. Medical Review. 2025;61(3):43-47.

[9] Heier JS, Clark WL, Boyer DS, et al. Intravitreal aflibercept injection for macular edema due to central retinal vein occlusion: two-year results from the COPERNICUS study. Ophthalmology. 2014;121:1414–1420.

[10] Chatziralli I, Machairoudia G, Kazantzis D, Theodossiadis G, Theodossiadis P. Inverted internal limiting membrane flap technique for myopic macular hole: a meta-analysis. Surv Ophthalmol. 2021 Sep-Oct;66(5):771-780. doi:10.1016/j.survophthal.2021.02.010. Epub 2021 Feb 27. PMID: 33652002.

[11] Markov G, Emin M, Zdravkov Y, Oscar A. Traumatic macular hole and uveitis: a case report. Sriwijaya J Ophthalmol. 2023;6(2):279-282. doi:10.37275/sjo.v6i2.110.

[12] Ebrahimi Z, Torkashvand A, Zarei M, Faghihi H, Khalili Pour E, Imani Fooldi M, Ebrahimiadib N. Treatment of inflammatory macular hole: case series and review of literature. Ocul Immunol Inflamm. 2022 May 19;30(4):966-972. doi:10.1080/09273948.2020.1867871. Epub 2021 Apr 7. PMID: 33826475.

[13] Ando T, Ueno A, Kawakami T. Macular hole with retinal pigment epithelium tear after anti-VEGF therapy in an eye with neovascular age-related macular degeneration. Am J Ophthalmol Case Rep. 2024;36:102126.

[14] Clemens CR, Eter N, Wenzel A. Macular hole formation in the presence of a pigment epithelial detachment after three consecutive intravitreal antivascular endothelial growth factor injections. J Ocul Pharmacol Ther. 2010;26(3):297-299.

[15] Grigoropoulos V, Katsimbris I, Apatzidou D. Full-thickness macular hole after intravitreal injection of ranibizumab in a patient with retinal pigment epithelium detachment and tear. Eur J Ophthalmol. 2010;20(2):469-472.

[16] Kabanarou SA, Wong D, Hollick EJ. Full-thickness macular hole formation following anti-VEGF injections for neovascular age-related macular degeneration. Clin Interv Aging. 2017;12:911-915.

[17] Gaudric A, Haouchine B, Massin P, Paques M, Blain P, Erginay A. Macular hole formation: new data provided by optical coherence tomography. Arch Ophthalmol. 1999;117(6):744–751.

[18] Tanner V, Chauhan DS, Jackson TL, Williamson TH. Optical coherence tomography of the vitreoretinal interface in macular hole formation. Br J Ophthalmol. 2001;85(9):1092–1097.

[19] Mojana F, Cheng L, Bartsch DU, et al. The role of abnormal vitreomacular adhesion in age-related macular degeneration: spectral optical coherence tomography and surgical results. Am J Ophthalmol. 2008;146(2):218–227. doi:10.1016/j.ajo.2008.04.027.

[20] Mukherjee C, Tewari A, Banerjee N. Macular hole formation after intravitreal ranibizumab injection in wet age-related macular degeneration. Open Ophthalmol J. 2015;9:177.

[21] Oshima Y, Murakami T, Sawa M. Full-thickness macular hole case after intravitreal aflibercept treatment. BMC Ophthalmol. 2015;15:30.

[22] Raiji VR, Eliott D, Sadda SR. Macular hole overlying pigment epithelial detachment after intravitreal injection with ranibizumab. Retin Cases Brief Rep. 2013;7(1):91-94. doi:10.1097/ICB.0b013e31826f090d.