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Case Report

Unexpected Vision Loss following Six Intravitreal Injections for Neovascular Age-Related Macular Degeneration

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Keywords

Age-related macular degeneration · Intravitreal injection · Macular hole · Optical coherence tomography · Vitreomacular traction

Abstract

Introduction: We present a case of a patient with preceding vitreomacular traction (VMT) who developed a full-thickness macular hole (FTMH) following his sixth intravitreal aflibercept injection for the treatment of age-related macular degeneration and review the literature on risk factors and pathogenesis of this adverse event. ***Case Presentation:*** FTMH can occur after an extended number of repeat intravitreal injections in the setting of worsening vitreomacular adhesion or VMT. This patient's FTMH was successfully treated surgically in a timely manner, and additional injections were resumed safely. ***Conclusions:*** Patients with an unexpected decrease in vision after intravitreal injections should be reevaluated with optical coherence tomography to rule out alternative pathology including vitreomacular interface abnormalities. FTMH, if present, should be treated promptly to allow for resumption of therapy as needed and visual optimization.

Introduction

Idiopathic full-thickness macular holes (FTMHs) typically occur over age 55 years, and their pathogenesis includes contraction of the pre-foveal vitreous cortex creating focal tangential and oblique traction on the fovea, as well as oblique and anterior posterior

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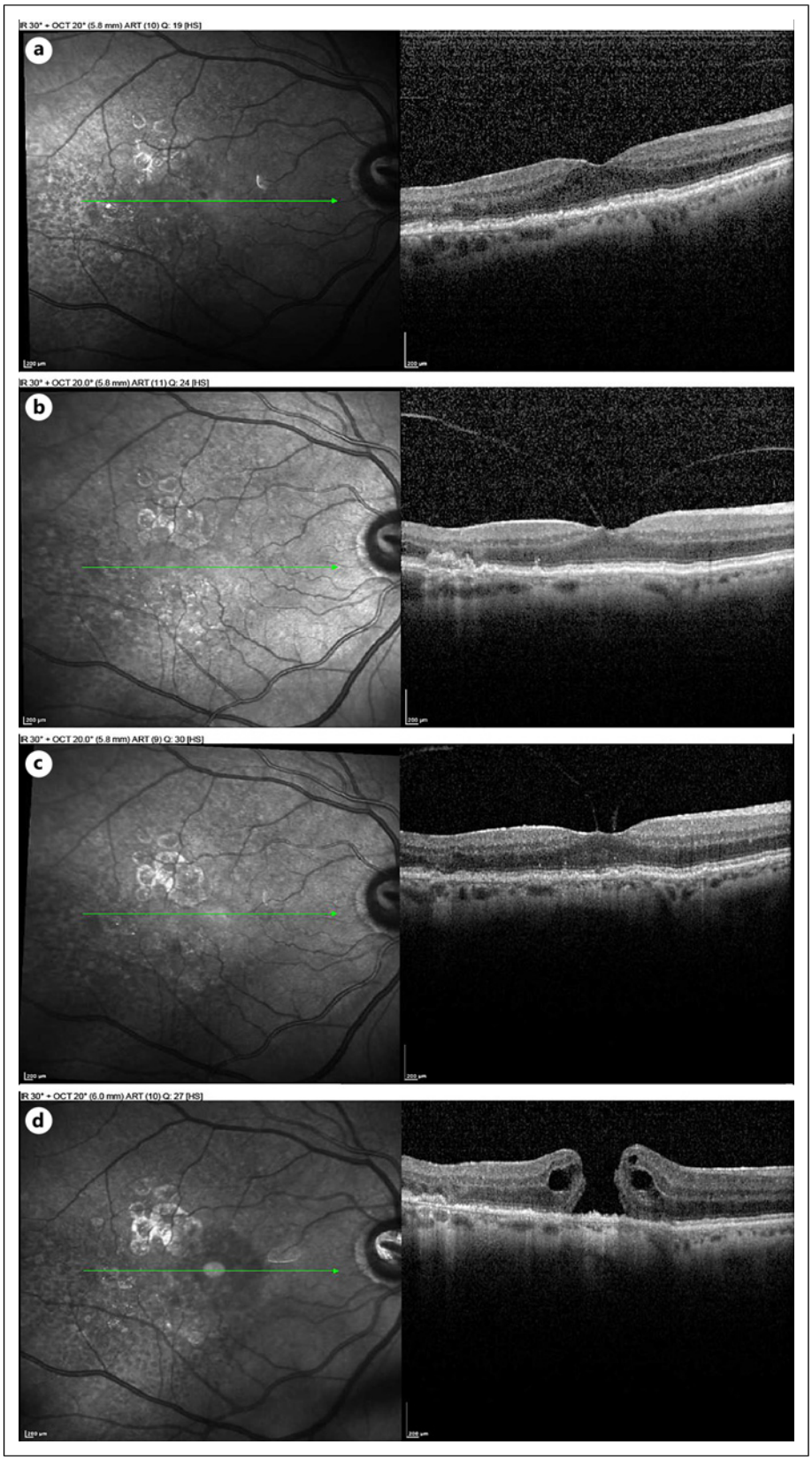

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tractional forces from an evolving posterior vitreous detachment (PVD) [1–3]. Epidemiological studies have shown that postmenopausal women have greater incidence of FTMHs, presumably due to decreases in estrogen leading to vitreous contraction [4]. To our knowledge, only 9 cases of FTMH formation after intravitreal aflibercept injection have been reported [5–11]. Multiple studies have delineated the capability of optical coherence tomography (OCT) in accurately diagnosing retinal pathologies such as PVD [12], subretinal hemorrhage [13], outer retinal hyperreflective deposits [14], and optic disk pit maculopathy [15]. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000537777).

Case Report

An undomiciled 83-year-old man with nAMD lost to follow-up for over a year presented to the West Los Angeles Veterans Affairs Medical Center with decreased vision in his right eye (OD). Past ophthalmic history includes nAMD in the left eye (OS) and uncomplicated cataract surgery in both eyes (OU) 6 years ago. Best corrected visual acuity (BCVA) was 20/60 OD and count fingers at 1 foot OS. Intraocular pressures were 13 mm Hg OD and 12 mm Hg OS.

Biomicroscopic examination was notable for two small macular hemorrhages OD and multiple macular drusen OU. OCT demonstrated intraretinal fluid, vitreomacular adhesion (VMA), and drusen OD (shown in Fig. 1a), and intraretinal fluid over a disciform scar OS. After discussion of risks and benefits of treatment, the patient decided to proceed with intravitreal aflibercept in OD, for which he returned at 2–3 month intervals. After the third and fourth aflibercept injection OD, progression of VMA was noted on OCT (shown in Fig. 1b, c).

Two and a half months after the sixth aflibercept injection OD, the patient returned with a subjective complaint of decreased vision OD, which, upon further questioning, started 2 weeks following his last injection. His BCVA OD had declined to 20/200 and OCT revealed a FTMH (shown in Fig. 1d). Following informed consent, the patient underwent prompt treatment with 25-gauge pars plana vitrectomy, internal limiting membrane peeling, and 20% SF6 gas injection OD with face down positioning for 1 week. On postoperative day 8, his vision improved to 20/80-2 and an OCT confirmed macular hole closure (shown in Fig. 2a).

One month following vitrectomy, the patient resumed aflibercept injections at 6-week intervals. Reevaluations over a 15-month follow-up period revealed no recurrence of FTMH (shown in Fig. 2b–e). His postoperative BCVA returned to his baseline 20/60.

Discussion

Only 9 cases of FTMH formation after intravitreal aflibercept injection have been reported [5–11]. Four cases had preexisting vitreomacular traction (VMT) [5, 6], one had a retinal pigment epithelium tear (RPE tear) [7], and one had both pigment epithelial detachment (PED) and new PVD [9] (online suppl. Table 1). All of these cases occurred after 1–3 injections,

Fig. 1. a Optical coherence tomography (OCT) of the right eye before treatment demonstrated non-center involving intraretinal fluid, VMA, and drusen. Best corrected visual acuity (BCVA) was 20/60 in the right eye and count fingers at 1 foot in the left eye. **b** OCT after the third aflibercept injection in the right eye showed progression of VMA. **c** OCT after the fourth aflibercept injection showed progression of VMA to VMT with tenting of the fovea. **d** OCT two and a half months after the sixth aflibercept injection revealed a FTMH. BCVA in the right eye was 20/200.

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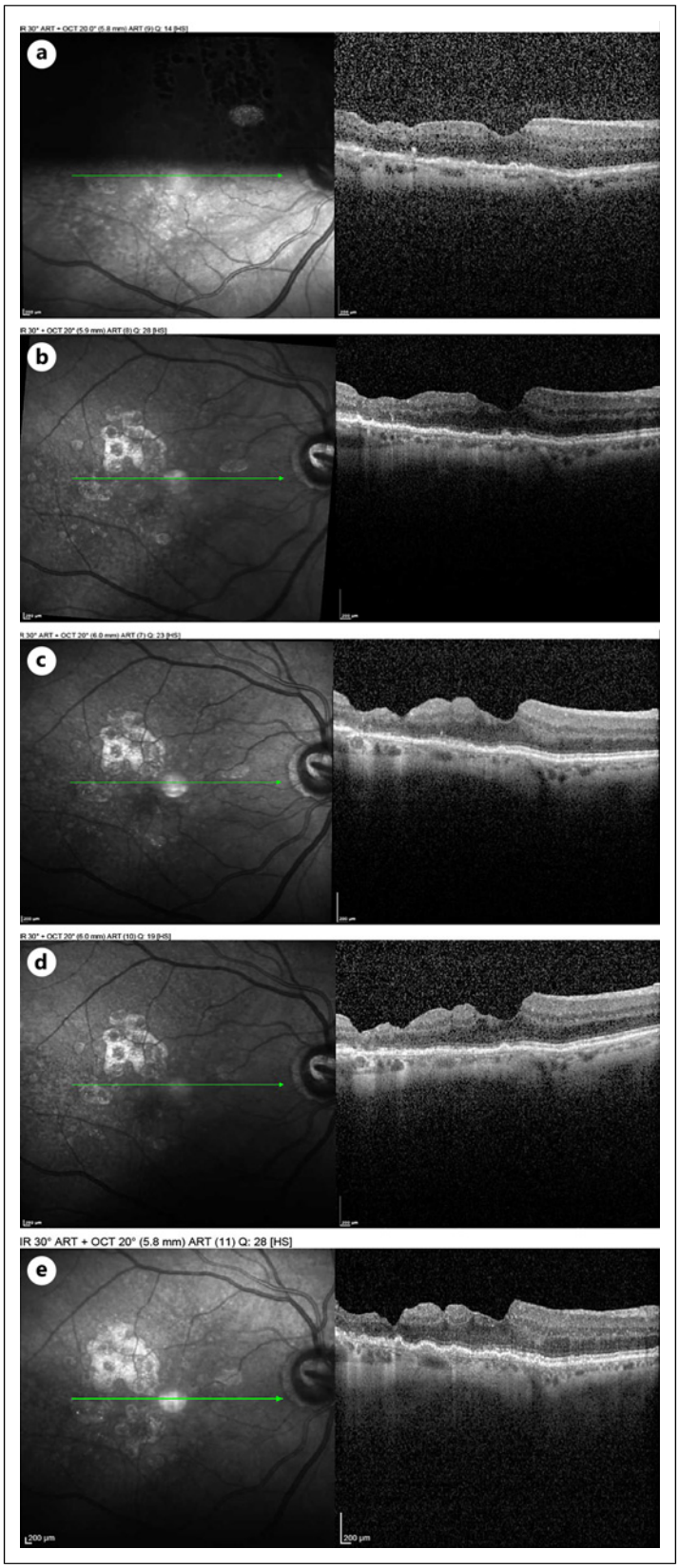

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in 4 females and 5 males with mean age of 72.4 ± 8.5 years. Our case reports the highest number of injections associated with this adverse event with FTMH developing after the sixth intravitreal injection. VMA, which is defined as perifoveal vitreous separation with remaining vitreomacular attachment and unperturbed foveal morphologic features, was documented on OCT prior to the first intravitreal injection (shown in Fig. 1a) [16]. After the third injection, worsening VMA was noted on OCT (shown in Fig. 1b). At the sixth injection, VMT, defined as anomalous PVD accompanied by anatomic distortion of the fovea, was noted (shown in Fig. 1c) [16]. Two weeks after the sixth injection, symptoms of FTMH developed (shown in Fig. 1d). This timeline suggests that gradually worsening VMT in the setting of repeated intravitreal injections eventually exerted sufficient traction on the fovea to result in a FTMH. Our case indicates FTMH can occur after an extended number of repeat intravitreal injections in the setting of VMA/VMT and the importance of using OCT to check for progression of disease and alternative macular pathology if a patient returns with an interval, unexpected vision deficit.

FTMH formation has been reported after injection of other anti-VEGF agents aside from aflibercept, including ranibizumab, bevacizumab, conbercept, and an unspecified anti-VEGF agent, as well as other agents including ocriplasmin, dexamethasone, and triamcinolone (online suppl. Table 2). Thirty-eight of the 50 eyes had preexisting pathologies that affected the vitreoretinal interface, including 20 eyes with a fluctuating PED or RPE tear, 8 eyes with VMA or VMT, 4 eyes with new onset PVD, 3 eyes with contracting epiretinal membrane (ERM), 2 eyes with both contracting ERM and fluctuating PED, and 1 eye with both PED and VMA (online suppl. Table 2). The association of FTMH formation with seven different injection agents both with and without anti-VEGF properties suggests that it is less likely a specific agent itself that is causing the FTMH. Rather, FTMH may result from evolving VMT, ERM formation, or a combination of the two, potentially contributing to the effect of intravitreal medications on the fluid and fibrovascular status of the retina and adjacent anatomic layers.

Adverse effects from intravitreal injections with anti-VEGF agents, as per product information provided by their manufacturers [17–19], do not include FTMH formation. Ophthalmologists should consider these agents' potential role in the pathogenesis of FTMH, particularly in the setting of preexisting VMA/VMT, PED/RPE tear, new-onset PVD, and contracting ERM. The benefits of anti-VEGF injections in our patient still outweighed potential risks, including any potential contribution to his FTMH given the relative rarity of this potential adverse reaction and the favorable surgical outcomes.

When consenting patients with nAMD for intravitreal injections, ophthalmologists should explain the risk of macular hole formation to patients, especially patients with history of vitreoretinal interface pathologies. Although it is more likely for this adverse event to occur in the beginning of the injection series, it can still occur after a number of repeated injections as seen in this case report. As such, patients should be advised after each injection visit to return immediately for any changes in vision so they can be promptly evaluated with OCT.

OCT is useful for identifying various retinal pathologies. Major OCT modalities include swept source (SS) and spectral domain (SD) OCT with and without enhanced depth imaging (EDI). SS-OCT without EDI or frame averaging (DRI OCT-1) and SD-OCT using EDI and frame

Fig. 2. a Optical coherence tomography (OCT) obtained on postoperative day 8 demonstrated successful closure of a FTMH. BCVA on postoperative day 8 was 20/80-2 in the right eye and count finger at 3 feet in the left eye. One month following successful vitrectomy, the patient resumed aflibercept injections at 6 weeks intervals. OCT at postoperative month 2 (**b**), month 5 (**c**), month 8 (**d**), and 1 year 3 months (**e**) revealed progression of post-ILM peel and AMD-associated atrophy temporally, and no macular hole recurrence. Visual acuity returned to the patient's baseline of 20/60.

averaging (SPECTRALIS) have similar signal penetration depths, while SD-OCT without EDI/frame averaging (Cirrus) has statistically significantly lower penetration depths. In addition, both SD-OCT using EDI/frame averaging and SS-OCT offer excellent visibility and contrast of the choroidoscleral junction [20]. Multiple studies have also delineated the capability of OCT in accurately diagnosing retinal pathologies such as PVD [12], subretinal hemorrhage [13], outer retinal hyperreflective deposits [14], and optic disk pit maculopathy [15]. Ophthalmologists should ensure proper OCT modalities are used at their clinics for optimal detection of macular holes. For most clinical applications, SD-OCT is standard of care, and SS-OCT is not necessary at this time.

Prompt surgical intervention likely contributed to the success of our patient's FTMH closure. This is supported by a study of idiopathic FTMH that found shorter duration of symptoms to be a significant predictor of visual success after vitrectomy and gas or air tamponade [21]. This is also the first case report that provides serial OCTs up to 1 year and 3 months after surgical repair of FTMH with resumption of injection 1 month after repair, demonstrating that long-term subsequent injections may be safely resumed postoperatively.

Conclusions

FTMH can occur after an extended number of repeat intravitreal injections in the setting of worsening VMA or VMT. Prompt vitrectomy with ILM peeling and gas was successful in this case, and long-term subsequent injections were safely resumed postoperatively. Patients who receive intravitreal injections and present with a sudden vision decline should be reevaluated with OCT to rule out this unexpected complication.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Hui, Gunzenhauser, and Tsui contributed to design of the manuscript, acquisition, analysis, and interpretation of the data, and drafting and reviewing of the work. Dillon contributed to interpretation of the data and reviewing of the work.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

References

1 Smiddy WE, Flynn HW. Pathogenesis of macular holes and therapeutic implications. Am J Ophthalmol. 2004; 137(3):525–37. https://doi.org/10.1016/j.ajo.2003.12.011
2 Gass JD. Idiopathic senile macular hole: its early stages and pathogenesis. Retina. 1988;106(5):629–39. https://doi.org/10.1001/archopht.1988.01060130683026
3 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):744–51. https://doi.org/10.1001/archopht.117.6.744
4 Ali FS, Stein JD, Blachley TS, Ackley S, Stewart JM. Incidence of and risk factors for developing idiopathic macular hole among a diverse group of patients throughout the United States. JAMA Ophthalmol. 2017;135(4): 299–305. Erratum in: JAMA Ophthalmol. 2017 Apr 1;135(4):404. https://doi.org/10.1001/jamaophthalmol.2016.5870
5 Ali Said Y, Vanwynsberghe D, Jacob J. Macular hole formation following intravitreal aflibercept for neovascular age-related macular degeneration. Case Rep Ophthalmol. 2022;13(1):247–52. https://doi.org/10.1159/000521975
6 Karamitsos A, Sorkou KN, Bhagey J, Hillier RJ, Papastavrou VT. An uncommon aflibercept side effect: full thickness macular hole formation after intravitreal injections in patients with pre-existing vitreomacular traction. Cureus. 2021;13(1):e12872. https://doi.org/10.7759/cureus.12872
7 Oshima Y, Apte RS, Nakao S, Yoshida S, Ishibashi T. Full thickness macular hole case after intravitreal aflibercept treatment. BMC Ophthalmol. 2015;15:30. https://doi.org/10.1186/s12886-015-0021-3
8 Hirata A, Hayashi K, Murata K, Nakamura KI. Removal of choroidal neovascular membrane in a case of macular hole after anti-VEGF therapy for age-related macular degeneration. Am J Ophthalmol Case Rep. 2018;9:14–7. https://doi.org/10.1016/j.ajoc.2017.12.003
9 Kabanarou SA, Xirou T, Mangouritsas G, Garnavou-Xirou C, Boutouri E, Gkizis I, et al. Full-thickness macular hole formation following anti-VEGF injections for neovascular age-related macular degeneration. Clin Interv Aging. 2017;12:911–5. https://doi.org/10.2147/CIA.S135364
10 Nowosielska A. Macular hole surgery in the case of wet age-related macular degeneration treated with intravitreal aflibercept. Case Rep Ophthalmol. 2019;10(3):369–73. https://doi.org/10.1159/000503415
11 Lee G, Lee S. Full-thickness macular hole after intravitreal aflibercept injection in a patient with wet age-related macular degeneration. J Korean Ophthalmol Soc. 2017;58(7):875–8. https://doi.org/10.3341/jkos.2017.58.7.875
12 Zvorničanin J, Zvorničanin E, Popović M. Accuracy of biomicroscopy, ultrasonography and spectral-domain OCT in detection of complete posterior vitreous detachment. BMC Ophthalmol. 2023;23(1):488. https://doi.org/10.1186/s12886-023-03233-4
13 Iglicki M, Khoury M, Donato L, Quispe DJ, Negri HP, Melamud JI. Comparison of subretinal aflibercept vs ranibizumab vs bevacizumab in the context of PPV, pneumatic displacement with subretinal air and subretinal tPA in naïve submacular haemorrhage secondary to nAMD. "The Submarine Study". Eye. 2024;38(2):292–6. https://doi.org/10.1038/s41433-023-02676-9
14 Iglicki M, Loewenstein A, Barak A, Schwartz S, Zur D. Outer retinal hyperreflective deposits (ORYD): a new OCT feature in naïve diabetic macular oedema after PPV with ILM peeling. Br J Ophthalmol. 2020;104(5):666–71. https://doi.org/10.1136/bjophthalmol-2019-314523
15 Iglicki M, Busch C, Loewenstein A, Fung AT, Invernizzi A, Mariussi M, et al. Underdiagnosed optic disk pit maculopathy: spectral domain optical coherence tomography features for accurate diagnosis. Retina. 2019; 39(11):2161–6. https://doi.org/10.1097/IAE.0000000000002270
16 Duker JS, Kaiser PK, Binder S, de Smet MD, Gaudric A, Reichel E, et al. The International Vitreomacular Traction Study Group classification of vitreomacular adhesion, traction, and macular hole. Ophthalmology. 2013; 120(12):2611–9. https://doi.org/10.1016/j.ophtha.2013.07.042
17 EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. 2023.
18 LUCENTIS® (ranibizumab) Injection full U.S. Prescribing Information. Genentech, Inc. 2018.
19 AVASTIN® (bevacizumab) Injection full U.S. Prescribing Information. Genentech, Inc. 2009.
20 Waldstein S, Faatz H, Szimacsek M, Glodan AM, Podkowinski D, Montuoro A, et al. Comparison of penetration depth in choroidal imaging using swept source vs spectral domain optical coherence tomography. Eye. 2015; 29(3):409–15. https://doi.org/10.1038/eye.2014.319
21 Steel DH, Donachie PHJ, Aylward GW, Laidlaw DA, Williamson TH, Yorston D; BEAVRS Macular hole outcome group. Factors affecting anatomical and visual outcome after macular hole surgery: findings from a large prospective UK cohort. Eye. 2021;35(1):316–25. https://doi.org/10.1038/s41433-020-0844-x