Case Report

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

Yasmin Ali Saida David Vanwynsbergheb Julie Jacoba

aDepartment of Ophthalmology, University Hospitals Leuven, Leuven, Belgium; bDepartment of Ophthalmology, Maria Middelares Hospital, Ghent, Belgium

Abstract

This case report describes full-thickness macular hole formation after intravitreal aflibercept injections for the treatment of macular neovascularization in neovascular age-related macular degeneration (AMD). Only limited case reports and case series have reported this possible adverse event after aflibercept injection. Possible mechanisms leading to the formation of a macular hole subsequent to intravitreal injection are focal tractional forces on the vitreoretinal interface due to globe deformation during needle insertion, vitreous syneresis, and vitreous incarceration at the injection site, and tangential shearing forces on the posterior surface of the retina due to contraction and rapid volume reduction of the neovascular membrane or a decrease in intra- or subretinal fluid. Furthermore, some reports suggest a toxic effect of the anti-vascular endothelial growth factor agent on a previously compromised retina as etiological factor. Macular hole formation may thus represent a rare adverse event of intravitreal aflibercept injection in patients with neovascular AMD, and it should be included in the differential diagnosis of post-injectional visual loss.

Introduction

Age-related macular degeneration (AMD) is a leading cause of visual impairment and severe vision loss in the elderly population worldwide. In neovascular AMD, severe visual impairment is often due to the development of macular neovascularization (MNV). In order to prevent further vision loss or possibly improve vision in patients with neovascular AMD, intravitreal anti-vascular endothelial growth factor (VEGF) therapy is now the major treatment...
leading to a decrease in legal blindness and visual impairment since the introduction. Aflibercept (Eylea®; Bayer HealthCare, Berlin, Germany, and Regeneron Pharmaceuticals, Tarrytown, PA, USA) is one of the two FDA-approved anti-VEGF agents for neovascular AMD. It is a recombinant protein composed of the binding domains of two human VEGF receptors 1 and 2 fused to the Fc region of human immunoglobulin gamma 1 [1]. In the eye, aflibercept blocks all VEGFA isoforms and VEGFB. Although anti-VEGF therapy is an effective treatment for MNV and macular edema in neovascular AMD, myopic choroidal neovascularization, polypoidal choroidal vasculopathy, retinal vein occlusion, etc., a limited number of ocular adverse events including endophthalmitis, increased intraocular pressure, retinal tear or detachment, retinal pigment epithelium tear, retinal ischemia, traumatic cataract, uveitis, and vitreous hemorrhage have been reported [2]. Full-thickness macular hole (FTMH) formation following intravitreal injections is rare and has only been reported in a few case reports and case series, mostly in association with neovascular AMD and in the presence of vitreomacular traction (VMT) disease [3–20]. Herein, we present a patient who developed a FTMH following intravitreal aflibercept injections for the treatment of MNV associated with AMD.

**Case Report**

A 71-year-old woman presented at our hospital for a second opinion for neovascular AMD which was diagnosed 6 months before. After the initial diagnosis, anti-VEGF injections were planned, but the patient refused treatment at that point. She had no specific ophthalmological history except for uncomplicated cataract surgery in both eyes about one and a half year earlier.

At presentation, best corrected visual acuity, as measured with a Snellen chart, in the right eye was 20/80 and in the left eye 20/33. Fundoscopic examination revealed, respectively, macular fibrosis and macular drusen with alterations of the retinal pigment epithelium (shown in Fig. 1a). Optical coherence tomography (OCT) displayed a hyperreflective pigment epithelial detachment (PED) with an overlying neurosensory retinal detachment (NSD) and an incomplete posterior vitreous detachment (PVD) with focal (≤1,500 µm) VMT in both eyes (shown in Fig. 2a). Fluorescein angiography showed central stippled hyperfluorescence in both eyes in the early phase with staining compatible with a fibrovascular membrane in the right eye and pinpoint leakage compatible with a type 1 MNV in the left eye in the late phases (shown in Fig. 1b). In order to treat the exudative AMD, we decided to give an induction treatment with three aflibercept injections at 4-week intervals in both eyes. After discussion of the potential benefits and side effects of the treatment, the patient gave her informed consent to undergo the intravitreal aflibercept injections, which were performed uneventfully.

Four weeks after the last intravitreal injection of aflibercept, the patient reported a central scotoma and best corrected visual acuity of the right eye had worsened to 20/200. OCT showed a large FTMH (475 µm) with raised edges and intraretinal cysts in the inner retina and a complete PVD. There was a resolution of the NSD. The left eye also had a resolution of the latter with a small persistent PED and VMT (shown in Fig. 2b). Surgical repair of the macular hole was suggested, but the patient chose not to undergo any operation.

**Discussion**

Until now, only a few cases describe FTMH formation as a cause of visual decrease after intravitreal injection of anti-VEGF agents for neovascular AMD, like ranibizumab (sixteen cases) [3–13] and bevacizumab (two cases) [14, 15]. Eight cases were reported after aflibercept intravitreal injection [10, 16–20].
Several mechanisms have been suggested in FTMH formation. In 1988, Gass [21] hypothesized that an idiopathic FTMH was the result of contraction of the prefoveal vitreous cortex leading to focal tangential traction on the fovea. Later, OCT studies by Gaudric et al. [22] and Tanner et al. [23] concluded that vitreous traction on the fovea may be oblique and that anteroposterior traction...
may lead to macular hole formation. Therefore, anteroposterior or oblique as well as tangential vitreous traction have been implicated as important factors of idiopathic FTMH formation. As suggested by Grigoropoulos et al. [6], globe deformation during needle insertion and vitreous syneresis, as well as vitreous incarceration at the injection site with possible peripheral vitreous pull, could account for anteroposterior traction at the vitreoretinal interface causing a FTMH [3]. In our case, focal VMT was documented on OCT imaging prior to the first intravitreal injection which developed to a PVD after three injections strongly suggesting tractive forces playing a role in the formation of the macular hole. Incomplete PVD, which can be induced by intravitreal injections, may create focal sites of traction on the retinal surface, and in the presence of pre-existing vitreomacular adhesion, this may increase the chances of developing a macular hole [4, 14]. However, other case reports with PVD prior to macular hole formation suggest there are additional mechanisms. It has been suggested that aflibercept itself may have led to macular hole formation by modulating the activity of the MNV inducing contraction and rapid volume reduction of the vascular membrane and decrease in intra- or subretinal fluid leading to tangential shearing forces on the posterior surface of the retina [14]. In addition, the presence of a PED has been mentioned to be a potential predisposing factor for the development of a macular hole after intravitreal injections for neovascular AMD. Changes in the size of a subfoveal PED could make the overlying retina more susceptible to tractive forces leading to a FTMH [10]. This hypothesis is supported by the fact that the number of case reports consisting of macular hole formation after intravitreal anti-VEGF or steroids used in MNV-associated diseases, we found, was higher than those without underlying MNV and only scarce number of cases in the literature describe macular hole formation after intravitreally injected substances for diseases without vascular component. Macular hole progression after ocriplasmin for enzymatic vitreolysis in symptomatic VMT and macular hole was reported as a complication [24]. We found no reports of FTMH formation after intravitreal
antibiotics or gas. Nevertheless, these still remain case reports and series and further investigation with larger sample size should confirm this.

Alternatively, some reports suggest the macular hole was caused by toxicity of the anti-VEGF on a previously compromised retina, although this looks less likely to be the cause because several studies found no toxic effect of anti-VEGF on the retina [14]. In addition, FTMH formation has been reported in case reports and series after other agents including bevacizumab, ranibizumab, conbercept, triamcinolone, tissue plasminogen activator in the treatment of intra- and/or subretinal fluid/hemorrhage due to proliferative diabetic retinopathy, retinal vein occlusion, myopic choroidal neovascularization, polypoidal choroidal vasculopathy, and rupture of retinal arterial macroaneurysm. This strongly suggests toxicity of aflibercept is not the main cause of the FTMH formation in our case, but a decrease in macular thickness and contraction of subretinal structures are more significant factors contributing to tractional forces on the overlying retina [10].

Conclusion

In conclusion, macular hole formation seems to be a potential complication after intraocular aflibercept injection in neovascular AMD, especially in patients without PVD. Therefore, it should be included in the differential diagnosis of post-injectional visual loss. Although the well-established potential benefits of an intravitreal injection for neovascular AMD do not outweigh this rare risk, one may be more prudent in the presence of pre-existing VMT.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The report does not include personal information that could identify the patient directly or indirectly. This study protocol was reviewed and approved by the Ethics Committee Research University Hospitals Leuven (August 31, 2021), and the reporting and writing are all in compliance with the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received for this research or publication.

Author Contributions

Y. Ali Said collected the data and designed, drafted, and finalized the article. She also searched the literature on PubMed by choosing the following MeSH terms: macular hole, age-related macular degeneration, and intravitreal anti-VEGF. J. Jacob was responsible for medical follow-up and treatment and has seen the patient in most intervals. D. Vanwynsberghe and J. Jacob critically reviewed the several drafts, and all authors approved the final version of the manuscript and are accountable for all aspects of the work.
Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1. Sarwar S, Clearfield E, Soliman MK, Sadiq MA, Baldwin AJ, Hanout M et al. Aflibercept for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2016;2:CD011346.
2. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, Brown DM, Chong V, Nguyen QD et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the view studies. Ophthalmology. 2014;121(1):193–201.
3. Querques G, Souied EH, Soubrane G. Macular hole following intravitreal ranibizumab injection for choroidal neovascular membrane caused by age-related macular degeneration. Acta Ophthalmol. 2009;87(2):235–7.
4. Clemens CR, Holz FG, Meyer CH. 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):297–9.
5. Jo YJ, Kim KN, Lee JE, Kim JY. Macular hole following intravitreal ranibizumab injections for choroidal neovascularization. J Korean Ophthalmol Soc. 2011;61(5):774–8.
6. Grigoropoulos V, Emfietzoglou J, Nikolaidis P, Theodossiadis G, Theodossiadis P. 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):469–72.
7. Mukherjee C, Mitra A, Kumar NA, Elsherbiny S, Lip PL. Macular hole formation after intravitreal ranibizumab injection with exudative age-related macular degeneration. Open Ophthalmol J. 2015;9:177–80.
8. Regatieri CV, Duker JS. Bilateral macular hole after anti-vascular endothelial growth factor therapy in a patient with exudative age-related macular degeneration. Retin Cases Brief Rep. 2012;6(1):125–8.
9. Rajji VR, Elliott D, Sadda SR. Macular hole overlying pigment epithelial detachment after intravitreal injection with ranibizumab. Retin Cases Brief Rep. 2013;7(1):91–4.
10. 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.
11. Kal M, Biskup M, Mackiewicz J. The macular hole after intravitreal injections of ranibizumab in a patient with exudative age-related macular degeneration: a case study. Studia Medyczne. 2013;29:89–93.
12. Shiff OA, Katz MSJ. Surgical management of full-thickness macular hole superimposed on exudative age-related macular degeneration. Retin Cases Brief Rep. 2021;15(3):211–3.
13. Kim JM, Jang JW, Kyung SE, Chang MH. Macular hole after single intravitreal injection of ranibizumab in a patient with age-related macular degeneration. J Korean Ophthalmol Soc. 2013;54(7):1130–4.
14. Moisseiev E, Goldstein M, Loewenstein A, Moisseiev J. Macular hole following intravitreal bevacizumab injection in choroidal neovascularization caused by age-related macular degeneration. Case Rep Ophthalmol. 2010;1(1):36–41.
15. Tufan HA, Gencer B, Kara S. Macular hole after intravitreal bevacizumab injection for choroidal neovascularisation. Clin Exp Optom. 2014;97(2):178–80.
16. Oshima Y, Apte RS, Nakao S, Yoshida S, Ishibashi T. Full thickness macular hole case after intravitreal aflibercept treatment. BMC Ophthalmol. 2015;15:30.
17. 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.
18. 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.
19. Nowosielski 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.
20. 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. 2017;9:14–7.
21. Gass JD. Idiopathic senile macular holes. Its early stages and pathogenesis. Arch Ophthalmol. 1988;106(5):629–39.
22. 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.
23. 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):1092–7.
24. Chatziralli I, Theodossiadis G, Xanthopoulos P, Miligkos M, Sivaprasad S, Theodossiadis P. Ocriplasmin use for vitreomacular traction and macular hole: a meta-analysis and comprehensive review on predictive factors for vitreous release and potential complications. Graefes Arch Clin Exp Ophthalmol. 2016;254(7):1247–56.