Case report

Removal of choroidal neovascular membrane in a case of macular hole after anti-VEGF therapy for age-related macular degeneration

Akira Hirataa,b, Ken Hayashia, Kazuhisa Muratac, Kei-ichiro Nakamurab

a Hayashi Eye Hospital, Fukuoka, Japan
b Division of Microscopic and Developmental Anatomy, Department of Anatomy, Kurume University School of Medicine, Kurume, Japan
c Department of Ophthalmology, Saga University Faculty of Medicine, Saga, Japan

ARTICLE INFO

Keywords:
Macular hole
Vitrectomy
Choroidal neovascular membrane
Age-related macular degeneration
FIB/SEM

ABSTRACT

Purpose: The formation of macular hole after receiving anti-vascular endothelial growth factor (anti-VEGF) therapy is rare. We report a case of macular hole that occurred after intravitreal injection of an anti-VEGF agent for age-related macular degeneration (AMD) in a patient, who underwent vitrectomy combined with choroidal neovascularization (CNV) removal.

Observations: A 64-year-old female with AMD affecting her right eye received an intravitreal injection of an anti-VEGF agent. After treatment, we identified a full thickness macular hole (MH) that was associated with the rapid resolution of the macular edema and contraction of the CNV. After performing vitrectomy combined with CNV removal, the MH closed and her visual acuity improved. Examination of the removed CNV revealed a network of microvessels devoid of pericytes.

Conclusions and importance: The present findings suggest that rapid resolution of macular edema and contraction of the CNV and/or mild increase in the vitreous traction after anti-VEGF therapy could potentially cause MH. CNV removal via the MH may be an acceptable procedure, if the MH remains open, the CNV is of the classic type, and it spares a central portion of the fovea.

1. Introduction

Today, anti-vascular endothelial growth factor (anti-VEGF) therapy is the first choice for treating age-related macular degeneration, myopic neovascular maculopathy, macular edema secondary to branch retinal vein occlusion (BVO) or diabetic macular edema. Anti-VEGF therapy leads to inactivation of the CNV, resolution of the macula edema and improvement in the visual outcome. In contrast, anti-VEGF therapy can lead to several complications. Formation of macular hole (MH) after intravitreal injection of an anti-VEGF agent is a rare complication. Here, we evaluated a case of MH after anti-VEGF therapy for AMD in a patient who underwent vitrectomy combined with CNV removal. There was a good visual prognosis in the patient after the procedure.

2. Case report

A 64-year-old female, who had been suffering from a visual disturbance in her right eye for at least a month, was referred to us for treatment of her right eye in September 2016. Best-corrected visual acuity (BCVA) in her right eye was 20/100 and a conventional fundus examination indicated multiple drusen in both of her eyes. In her right eye, subretinal hemorrhage was associated with wet AMD (Fig. 1A). Fluorescein (FA) and indocyanine green (IA) angiography showed the presence of classic choroidal neovascularization (CNV) in the macula (Fig. 1B). Optical coherence tomography (OCT) indicated the presence of subretinal CNV and macular edema (Fig. 1C and D). After obtaining informed consent from the patient, an intravitreal aflibercept injection was administered. OCT revealed resolution of the macular edema and a reduction in the CNV following the first treatment (Fig. 1E and F). However, after performing the third injection, the formation of full-thickness MH was observed (Fig. 2A and B). Although the BCVA in her right eye remained stable, she complained of a worsening central scotoma. OCT angiographic image indicated that the CNV was located in the lower nasal area to the fovea and the base of the macular hole was partially covered by the edge of the CNV (Fig. 2C and D).

After discussing the available treatment options, the patient decided to undergo a vitrectomy combined with cataract surgery procedure in her right eye at ten weeks after the onset of the MH. After phacoemulsification and aspiration, an intraocular lens was implanted. Subsequently, we then performed a pars plana vitrectomy with a 25-
gauge trocar system (Video). Following core vitrectomy, peeling of the internal limiting membrane (ILM) was performed around the MH (Fig. 3A). The ophthalmic viscoelastic device was then slowly introduced into subfoveal space via the MH in order to create an artificial retinal detachment that was 1 disc diameter (DD). An additional 20-gauge port was made next to the right side trocar port in order to introduce a subretinal spatula that was used to detach the CNV from the retinal pigment epithelium (RPE) via the MH (Fig. 3B). The CNV was removed via the MH with 25G vitreous forceps (Fig. 3C). A 1.5 DD ILM flap was created in the temporal area and used to cover the macular area (Fig. 3D). The surgery was completed by fluid-air exchange and air tamponade, with the patient instructed to maintain a prone position for three days.

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.ajoc.2017.12.003.

The removed CNV was partially surrounded by RPE. Numerous microvessels were observed inside of the CNV (Fig. 4A). Ultrastructural examination by focused ion beam/scanning electron microscopy (FIB/SEM) revealed that there was a network of microvessels formed by vascular endothelial cells that was devoid of any association with pericytes (Fig. 4B).

At four days after the surgery, closure of the MH was observed. Fundus examination at four weeks after the surgery showed the presence of the focal RPE atrophy, which corresponded to the location of
the CNV (Fig. 4C). A subsequent OCT revealed closure of the MH and a focal defect of the ellipsoid zone (Fig. 4D and E). There was a reduction in the patient’s complaints and there was improvement of the BCVA in her right eye to 20/40. Eight months after the surgery, her visual acuity and fundus findings remained stable.

3. Discussion

MH after anti-VEGF therapy has been reported to occur in AMD, myopic CNV and BVO.2–6 Spontaneous closure of MH after CNV has also been reported.7 Since the MH remained unchanged for more than 2 months in our current case, it was necessary to perform vitrectomy.

There are several possible mechanisms that might be responsible for the formation of MH after anti-VEGF therapy including, 1) alteration of the vitreo-retinal interface due to inflammatory reactions related to exudative changes of AMD and/or intraocular inflammation by intravitreal injections of an anti-VEGF agent; 2) mild increase in the vitreous traction after repeated injections of an anti-VEGF agent; 3) changes in the retinal structure due to rapid resolution of the macular edema caused by the anti-VEGF therapy; and 4) tangential traction from the subretinal side due to contraction of the CNV after the therapy.8,9 However, it is also possible that the formation of the MH could have been completely unrelated to the anti-VEGF treatment.

It has been reported that the visual prognosis after surgery for MH associated with CNV is dependent upon the damage of the macula and RPE.10 In terms of the current case, the closure of the MH could have been achieved without CNV removal. However, since the visual acuity of the patient remained unchanged after anti-VEGF therapy, the subfoveal CNV was thought to be a major cause of the visual disturbance. Also, the patient’s preoperative FA and OCT findings showed that the CNV was of the predominantly classic type in addition to being located in the lower nasal area to the fovea. Furthermore, the base of the MH
was partially covered by the edge of the CNV. Previous multicenter trials that compared submacular surgery and observation for AMD have reported finding no benefits for the surgery with regard to the visual prognosis.\textsuperscript{11,12} Therefore, surgical removal of CNV is no longer performed for AMD at the present time. Problems of CNV removal could potentially include retinal tear formation during surgery, cataract progression, postoperative retinal detachment and bleeding, progressive RPE atrophy, and the late recurrence of CNV. Thus, this procedure has not been performed in our hospital for more than a decade. In contrast, other previous studies have reported finding stabilization of the AMD and improvement of the visual acuity of the patients, especially in the cases with classic CNV, although a selection bias could not be definitively ruled out.\textsuperscript{13–15} Based on these previous reports and the findings in the current case, we decided that the surgical removal of the CNV should be used as the following indications were found for the patient: 1) the CNV was of the classic type, 2) no additional retinal damage would be caused by retinotomy as the CNV removal was performed via the macular hole, 3) the procedure would lead to less risk of RPE damage during the CNV removal except at the site of the CNV, and 4) there would be less risk of bleeding during the CNV removal after the anti-VEGF therapy. Furthermore, because the half-life of the anti-VEGF agent is known to be shortened after vitrectomy,\textsuperscript{16} stabilization of the AMD by CNV removal would help to reduce the number of the anti-VEGF treatments required.

As a result, the CNV in our current case exhibited a reduction in size after the anti-VEGF therapy, there was less bleeding during the surgery, and it was easy to grasp the CNV via the MH. Moreover, by performing ILM peeling prior to the removal of the CNV, this may contribute to the elasticity of the retinal tissue, thereby reducing the retinal damage that occurs during the actual removal of the CNV.

To ensure there was closure of the MH, we created a large single ILM flap to cover the entire macula. As a result, we were able to achieve complete closure of the MH with air tamponade. Thus, this procedure may contribute to a good visual recovery by preventing the unnecessary use of folding smaller scraps of the ILM flap.

When the area of the removed CNV was observed by FIB/SEM, the images indicated that there was a network of newly formed microvessels that remained even after repeated anti-VEGF therapy. Therefore, CNV removal might be an alternative option to consider when treating selected cases of AMD.

4. Conclusions

In our current case, both MH closure and cure of the AMD were achieved by using vitrectomy combined with CNV removal. Even so, at the present time CNV removal is not considered to be a primary treatment option for AMD. However, if the formed MH remains open, the underlying CNV is predominantly classic and inactive, and the location of the CNV spares a significant portion of the fovea, as was seen in the current case, CNV removal may be an acceptable procedure for improving the visual function and managing the AMD.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Acknowledgements and disclosures

Funding

This work was supported by JSPS KAKENHI Grant Numbers JP15K10886 and JP16H06280.

Conflict of interest

The following authors have no financial disclosures: AH, KH, KM, KN.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Acknowledgements

None.

References

1. Falavarjani KG, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. Eye. 2013;27(7):787–794.
2. Oshima Y, Apte RS, Nakao S, Yoshida S, Ishibashi T. Full thickness macular hole case after intravitreal aflibercept treatment. BMC Ophthalmol. 2015;15:30.
3. Muramatsu D, Mitsuhashi R, Iwasaki T, Goto H, Miura M. Macular hole formation following intravitreal injection of ranibizumab for branch retinal vein occlusion: a case report. BMC Res Notes. 2015;8:358.
4. Clemens CR, Holz FG, Meyer CH. Macular hole formation in the presence of a pigment epithelial detachment after three consecutive intravitreal anti-vascular endothelial growth factor injections. J Ocul Pharmacol Ther. 2010;26(3):297–299.
5. Miura M, Iwasaki T, Goto H. Macular hole formation after intravitreal bevacizumab administration in a patient with myopic choroidal neovascularization. Retin Cases Brief Rep. 2011;5(2):149–152.
6. Mukherjee C, Mitra A, Kumar NA, Elsherbiny S, Lip PL. Macular hole formation after intravitreal ranibizumab injection in wet age-related macular degeneration. Open Ophthalmol J. 2015;9:177–180.
7. Chandhry NA, Tabanobe H, Flynn HWJ, Konjara V, Liggett PE. Spontaneous development and closure of full thickness macular hole during intravitreal anti-VEGF therapy for neovascular age-related macular degeneration. ARVO Annu Meet. 2012;53(14).
8. Okamoto T, Shihoda O, Kurihara T, Nagai N, Tsuhota K, Ozawa Y. Intraoperative and fluorescein angiographic findings of a secondary macular hole associated with age-related macular degeneration treated by pars plana vitrectomy. BMC Ophthalmol. 2014;14:114.
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):91–94.
10. Elsing SH, Postel EA, Gill MK, Jampol LM, Jaffe GJ. Management of eyes with both idiopathic macular hole and choroidal neovascularization. Retina. 2004;24(6):613–619.
11. Bressler NM, Bressler SB, Hawkins BS, et al. Submacular surgery trials randomized pilot trial of laser photoagulation versus surgery for recurrent choroidal neovascularization secondary to age-related macular degeneration: I. Ophthalmic outcomes submacular surgery trials pilot study report number 1. Am J Ophthalmol. 2000;130(4):387–407.
12. Submacular Surgery Trials Research Group. Submacular surgery trials randomized pilot trial of laser photoagulation versus surgery for recurrent choroidal neovascularization secondary to age-related macular degeneration: II. Quality of life outcomes submacular surgery trials pilot study report number 2. Am J Ophthalmol. 2000;130(4):408–418.
13. Guthoff R, Schrader W. Longterm results in surgical removal of subfoveal choroidal neovascularization in age-related macular degeneration. Acta Ophthalmol Scand. 2004;82:686–690.
14. Shimada H, Fujita K, Matsumoto Y, Mori R, YuzuwA M. Preoperative factors influencing visual outcome following surgical excision of subfoveal choroidal. Eur J Ophthalmol. 2006;16(2):287–294.
15. Falkner CI, Leitich H, Frommelt F, Bauer P, Binder S. The end of submacular surgery for age-related macular degeneration? A meta-analysis. Graefes Arch Clin Exp Ophthalmol. 2007;245(4):490–501.
16. Christoforidis JB, Williams MM, Wang J, et al. Anatomic and pharmacokinetic properties of intravitreal bevacizumab and ranibizumab after vitrectomy and lensectomy. Retina. 2013;33(5):946–952.