



Macular hole with retinal pigment epithelium tear after anti-VEGF therapy in an eye with neovascular age-related macular degeneration

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ARTICLE INFO

Keywords:

Age-related macular degeneration
Anti-vascular endothelial growth factor therapy
Macular hole
Pigment epithelial detachment
Retinal pigment epithelial tear

ABSTRACT

Purpose: To report a case of a full-thickness macular hole (FTMH) associated with a retinal pigment epithelium (RPE) tear after anti-vascular endothelial growth factor (anti-VEGF) therapy for neovascular age-related macular degeneration (nvAMD), which was successfully closed by vitreous surgery.

Observations: A 73-year-old man with nvAMD in the right eye received an intravitreal aflibercept injection due to enlarged pigment epithelial detachment. However, 2 days after the third injection, the patient experienced a sudden decline in vision. An FTMH with a tear in the underlying RPE was detected. The FTMH was closed using vitrectomy combined with the inverted internal limiting membrane (ILM) flap technique.

Conclusions and Importance: Our case highlights a rare complication of both an FTMH and an RPE tear after anti-VEGF therapy. Vitrectomy, with the inverted ILM flap technique, proved effective in closing the FTMH despite the complexity of the case.

1. Introduction

Anti-vascular endothelial growth factor (anti-VEGF) therapy has drastically improved visual outcomes in individuals with neovascular age-related macular degeneration (nvAMD).¹ However, a noteworthy complication of this therapy is pigment epithelial detachment (PED), which can result in retinal pigment epithelium (RPE) tear. If the tear affects the macula, it can lead to irreversible vision loss.^{1,2}

We present a case of a full-thickness macular hole (FTMH) and an RPE tear occurring after anti-VEGF therapy in an eye with PED associated with nvAMD. In our case, it was unusual for the RPE tear to have a star-shaped appearance, possibly caused by mechanical force, and to remain attached to the overlying photoreceptor cell layer while also coexisting with an FTMH.

While cases of FTMH above the PED that can be closed through anti-VEGF therapy or vitrectomy have been reported,^{3,4} vitrectomy successfully closed the FTMH in this specific combination and led to visual improvement.

2. Case report

A 73-year-old man had been regularly visiting another hospital for fundus examination since the age of 60 due to diabetes mellitus and hypertension. The patient had a history of smoking 20 cigarettes per day between the ages of 20 and 67 years. While fundus examination revealed no signs of diabetic retinopathy, optical coherence tomography (OCT) revealed irregularities in the RPE and multiple drusen in both eyes, leading to a diagnosis of early age-related macular degeneration (AMD). The best-corrected visual acuity (BCVA) was 20/13 in both eyes, with intraocular pressures of 12 mmHg for the right eye and 14 mmHg for the left eye. When the patient was 72 years old, a PED of 1.24 mm in the vertical axis and 1.59 mm in the horizontal axis appeared under the macula of the right eye, while visual acuity remained stable. Subsequently, the PED enlarged to 1.89 mm in the vertical axis and 2.28 mm in the horizontal axis. However, the vision was still preserved.

Fundus fluorescein angiography revealed leakage and pooling into the sub-PED space. Additionally, no polyp was found on indocyanine green angiography. These findings led to the diagnosis of type 1 macular neovascularization (type 1 MNV) (Fig. 1).

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<https://doi.org/10.1016/j.ajoc.2024.102126>

Received 22 September 2023; Received in revised form 26 June 2024; Accepted 12 July 2024

Available online 17 July 2024

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Intravitreal aflibercept (IVA) injection was administered to the right eye, after which the PED decreased in height. After the second monthly IVA, the BCVA was 20/17 in the right eye. However, within two days of the third IVA, the patient complained of vision loss. The fundus examination and OCT revealed significant enlargement of the PED, accompanied by an FTMH and an underlying RPE tear. The PED was remarkably increased by 10.3 mm in the vertical axis and 12.66 mm in the horizontal axis. An FTMH and an RPE tear, located just below the macula, were observed at the center of the PED. Unlike typical RPE tears that result in shrinkage, the RPE within the PED area remained attached to the photoreceptor cell layer (Fig. 2), while the BCVA in the right eye decreased to 20/133.

Three days after the third IVA, the patient was referred to our clinic, and the right eye underwent vitrectomy combined with cataract surgery on the same day. The vitrectomy was performed using the inverted internal limiting membrane (ILM) flap technique to achieve better anatomical and visual outcomes, and tamponade with 20 % sulfur hexafluoride gas was also applied. Intravitreal injections of any anti-VEGF drug were not administered intraoperatively. By the first postoperative month, the FTMH promptly closed; however, a flat PED remained outside the fovea. By the sixth postoperative month, the PED disappeared, and BCVA in the right eye improved to 20/29 (Fig. 3). At 12 months postoperatively, BCVA further improved to 20/25. The RPE defect caused by the RPE tear remained but did not expand postoperatively. No additional anti-VEGF therapy was administered postoperatively.

3. Discussion

We present a case of an FTMH and RPE tear after anti-VEGF therapy in an eye with enlargement of PED associated with nvAMD. The FTMH was successfully closed using vitrectomy with the inverted ILM flap technique, even in this specific combination.

RPE tears were first reported as a complication of PED associated with AMD by Hoskin et al.⁵ in 1981. In vascularized PEDs caused by type 1 MNV, retinal angiomatous proliferation, or polypoidal choroidal vasculopathy (PCV), RPE tears may develop in the natural course of the disease or in association with interventions such as photodynamic therapy and laser photocoagulation, as well as anti-VEGF therapy.

Recent research highlights the heightened risk of RPE tears

associated with anti-VEGF therapy. This increased risk can be attributed to various factors, such as the traction caused by the contraction of MNV, the tangential tension of RPE at the PED area, and the elevated internal pressure within the PED resulting from intravitreal injection and/or osmotic pressure alteration. Risk factors for RPE tears include a high PED, a small MNV to PED size ratio, microrips, and a short duration since PED development.¹

An FTMH is commonly caused by vitreous adhesions leading to tangential and vertical traction on the macula.^{6–9} Treatment typically involves vitrectomy, ILM peeling, and gas tamponade.¹⁰ Some reported cases of an FTMH with a PED suggest that the tangential forces exerted on the retina overlying PED might lead to macular hole (MH) development. Anti-VEGF therapy can result in PED resolution and MH closure, indicating that PED-associated tangential force may contribute to MH development.³

Conversely, there have been reported cases of MH occurring after anti-VEGF therapy in nvAMD patients with a PED.^{11–13} It is suggested that changes in AMD activity and intraocular inflammation following anti-VEGF treatment can alter the vitreoretinal surface, increase vitreous traction, reduce macular edema, and shrink the MNV, potentially leading to FTMH development. Therefore, it is important to be aware of the rare complication of MH development following anti-VEGF treatment.¹² Regarding the treatment of MH with a PED, Raiji et al.,¹³ Cazabon et al.,¹⁴ and Azuma et al.⁴ have reported on surgical approaches involving vitrectomy with ILM peeling.

In our case, both an FTMH and the underlying RPE tear developed after anti-VEGF therapy in nvAMD with a PED. While there are a few reports on FTMH accompanying RPE tears,^{15,16} the underlying mechanism remains unclear. Generally, RPE tears occur at the edge of the PED and shrink towards the contralateral side. Notably, in this case, the RPE tear occurred near the center, not at the edge of the PED, and the torn RPE did not shrink or detach from the retina. Both the star shape of the RPE tear and intraretinal hemorrhage at the edge of the FTMH suggested that mechanical force affected their development. Thus, a complex interplay of tangential forces between the macula and underlying RPE may be associated with the simultaneous development of an FTMH and an RPE tear. Factors such as increased intraocular pressure from intravitreal injection and changes in choroidal vascular permeability may have contributed to the enlargement of the PED, facilitating tangential traction on the RPE within the PED area and the overlying macula,

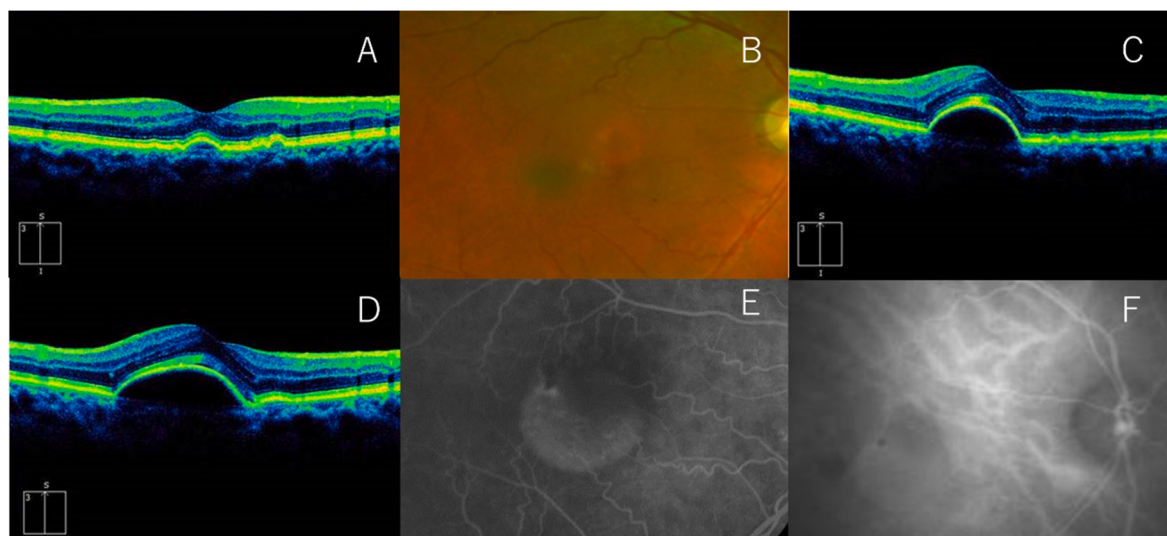


Fig. 1. A and B. Optical coherence tomography (OCT) vertical section and fundus photograph of the right eye. Drusen and irregular ridges of the retinal pigment epithelium (RPE) are visible. C. Right ocular OCT at 5 months after the initial image acquisition showing a pigment epithelial detachment (PED). D. Right ocular OCT at 11 months after the initial image acquisition, showing slight enlargement of the PED. E. Fluorescein angiography revealed leakage and pooling that increased in the late phase. F. Indocyanine green angiography showing no polypoidal lesions. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

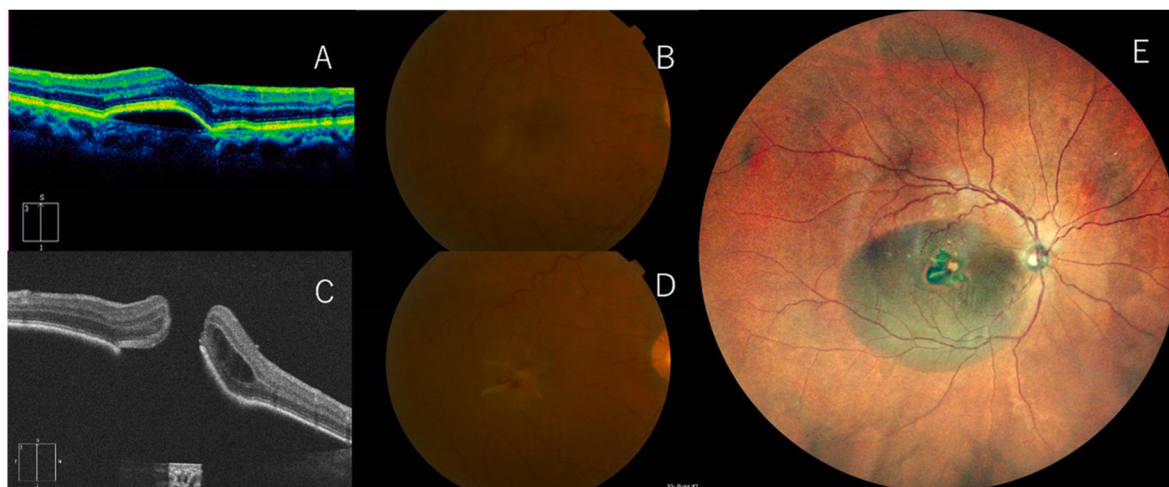


Fig. 2. **A and B.** Optical coherence tomography (OCT) and fundus photograph of the right eye before the third dose of intravitreal aflibercept (IVA). The pigment epithelial detachment (PED) is observed to have shrunk. **C and D.** OCT and fundus photograph 2 days after the third dose of IVA, showing a full-thickness macular hole with a retinal pigment epithelial (RPE) tear; the RPE remained attached to the retina without shrinkage. Additionally, the fundus photograph shows a radial RPE tear with intraretinal hemorrhage. The best-corrected visual acuity (BCVA) at this point is 20/120. **E.** The PED shows marked enlargement.

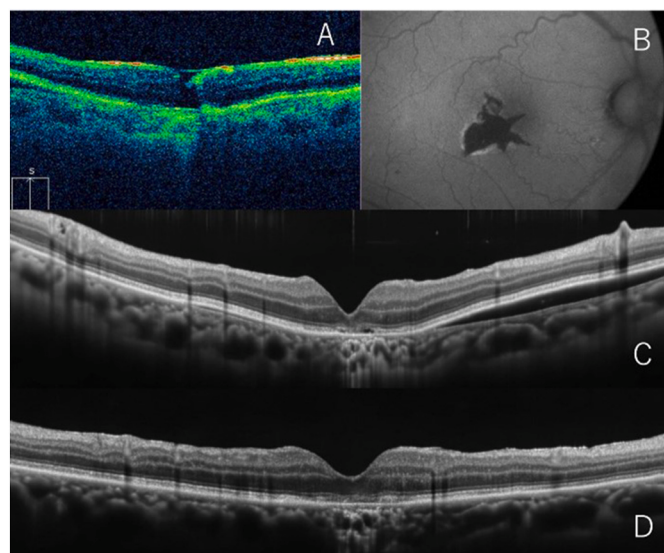


Fig. 3. Postoperative findings after vitrectomy. **A.** On the first day postoperatively, optical coherence tomography (OCT) shows cross-linking using the inverted internal limiting membrane (ILM) flap. **B.** Fundus autofluorescence at 1 month postoperatively. Starfish-shaped low autofluorescence indicates retinal pigment epithelium (RPE) deficiency. **C.** OCT at 2 months postoperatively. The macular hole (MH) is closed; however, the pigment epithelial detachment (PED) remains outside the fovea. The best-corrected visual acuity (BCVA) is 20/33. **D.** OCT at 6 months postoperatively reveals PED disappearance and 20/29 BCVA.

leading to an FTMH and an RPE tear.

Despite the complicated case of FTMH and an underlying RPE tear, vitrectomy combined with the inverted ILM flap technique can achieve MH closure. Fortunately, in this case, the RPE defect was slightly outside the fovea, and the patient maintained good vision. In the future, thorough examination is necessary to detect any potential recurrence of MH and nvAMD, as well as the progression of macular atrophy.

4. Conclusions

Our case involved a rare complication with both an FTMH and an underlying RPE tear that occurred following anti-VEGF therapy in an

nvAMD patient with a PED. Using vitrectomy with the inverted ILM flap technique, we successfully closed the MH. Notably, the RPE defect was fortunately positioned away from the fovea, contributing to the restoration of good vision. While the long-term prognosis remains uncertain, this surgical approach shows promise in preserving vision in complex cases. Continued vigilant monitoring is necessary to address future complications and mitigate the risk of vision loss.

Patient consent

The patient has given written consent for the publication of the case.

Funding

No funding or grant support was acquired to conduct this study.

Authorship

All authors state that they meet the current ICMJE criteria for authorship.

CRediT authorship contribution statement

Tomoko Ando: Writing – original draft, Investigation, Data curation. **Masaomi Kubota:** Writing – review & editing, Supervision, Project administration, Investigation. **Tsutomu Yasukawa:** Writing – review & editing, Supervision. **Taishi Miyase:** Investigation, Data curation. **Kiyona Ishiguro:** Investigation, Data curation. **Yuya Esaki:** Investigation, Data curation. **Aki Kato:** Writing – review & editing. **Satoko Kokuzawa:** Writing – review & editing. **Yoshio Hirano:** Writing – review & editing. **Hirokazu Sakaguchi:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

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