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Epiretinal Membrane – What does It Change in Anti-vascular Endothelial Growth Factor Therapy Injection (anti-VEGF)?

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Summary: Epiretinal membrane is a type of fibrous proliferation on the retinal surface in the macular region. Its most common symptoms include metamorphopsia, micropsia, macropsia, and reduced visual acuity. When these symptoms are present, patients are typically treated surgically with posterior vitrectomy. During the procedure, both the epiretinal membrane and the internal limiting membrane are removed. Postoperatively, an improvement in visual acuity and resolution of membrane-related symptoms are generally observed. A particular clinical challenge arises when epiretinal membrane coexists with diabetic macular edema or exudative age-related macular degeneration. In such cases, the membrane is believed to reduce the effectiveness of anti-vascular endothelial growth factor therapy. When these conditions coexist, surgical treatment may also be applied; however, outcomes are not always satisfactory. It is generally assumed that surgery should be performed at least after a loading phase of pharmacological therapy and, optimally, after a longer period if therapeutic effects remain insufficient. This paper reviews the available literature and presents clinical cases of patients treated with both surgical intervention and anti-vascular endothelial growth factor therapy.

Key words: epiretinal membrane, anti-vascular endothelial growth factor (anti-VEGF), vitrectomy, optical coherence tomography (OCT).

As early as 1865, Ivanov described the presence of fibrous proliferation on the surface of the internal limiting membrane (ILM) of the retina, today referred to as the epiretinal membrane (ERM). The cause of this pathology is usually idiopathic (95% of patients). In the remaining cases, it is classified as a secondary membrane: in diabetic retinopathy, central retinal vein occlusion, uveitis, following endophthalmitis, trauma, vitreoretinal surgery, or posterior vitreous detachment – as its elements called vitreous cortex remnants (VCR) [1]. ERMs occur bilaterally in 20% of cases. It is estimated that 20% of individuals over the age of 75 are affected. The Australian Blue Mountains Eye Study, conducted in a cohort of 3,654 participants, demonstrated ERM progression within one year in 20% of patients, regression in 26%, and stabilization in 39% [2]. Women are affected slightly more often than men, and the main symptoms include metamorphopsia, reduced visual acuity, micropsia or macropsia, and diplopia. Some patients, particularly in the early stages of the disease, may remain asymptomatic. The primary diagnostic tool is Optical Coherence Tomography (OCT). In symptomatic patients, surgical treatment with posterior vitrectomy with ERM and ILM removal is considered an effective and safe technique.

ERM in patients with diabetic macular edema

It is estimated that approximately 40% of patients with diabetic macular edema do not respond to anti-VEGF therapy (Vascular Endothelial Growth Factor – VEGF). Negative prognostic factors (with respect to improvement in visual acuity and reduction of central retinal thickness) include:

- presence of ERM or vitreomacular traction,
- serous retinal detachment,
- diffuse retinal thickening (so-called sponge-like edema),
- presence of hyperreflective foci,
- disrupted integrity of the junction between the inner and outer photoreceptor layers.

Poor response to anti-VEGF therapy is thought to be related, among other factors, to the presence of subclinical tractional forces or reduced oxygen diffusion between the retina and the vitreous body. It is believed that ERM may serve as a reservoir for VEGF, interleukin-6, and other proangiogenic inflammatory mediators. According to some authors, ERM is associated with mechanical retinal stretching that triggers cytokine release. It appears that the epiretinal membrane may act as a mechanical barrier, reducing the penetration of anti-VEGF agents to the outer retinal layers [3]. Lee et al. demonstrated that in patients with ERM, a greater number of intravitreal ranibizumab injections are required [4]. The treatment of choice is posterior vitrectomy with membrane peeling; however, it should be noted that removal of the vitreous body reduces the half-life of anti-VEGF agents, resulting in the need for more frequent injections, often at higher doses, in postoperative patients [5]. It has also been shown that in individuals with coexisting ERM and DME, macular peeling leads to significant improvement in best corrected visual acuity (BCVA) and a reduction in central retinal thickness [6]. However, the resolution of macular edema was not observed, which raises questions about the role of ERM as a mechanical barrier to anti-VEGF agents.

Patient 1

A 64-year-old male patient was scheduled for treatment of diabetic macular edema. At the start of therapy, his BCVA was 0.25, and central retinal thickness (CRT) was 567 μm (Fig. 1). The patient's diabetes was fairly well controlled (HbA1c = 6.3 mg%). The presence of ERM was observed. A series of five bevacizumab injections was administered (Fig. 1–5). However, neither visual acuity nor CRT improved (Fig. 5). A decision was made to proceed with surgical treatment, and a 25G vitrectomy with epiretinal membrane peeling was performed. After the procedure, the patient received a series of faricimab injections (Fig. 6–9). Following this treatment, visual acuity improved and the macular edema nearly completely resolved.

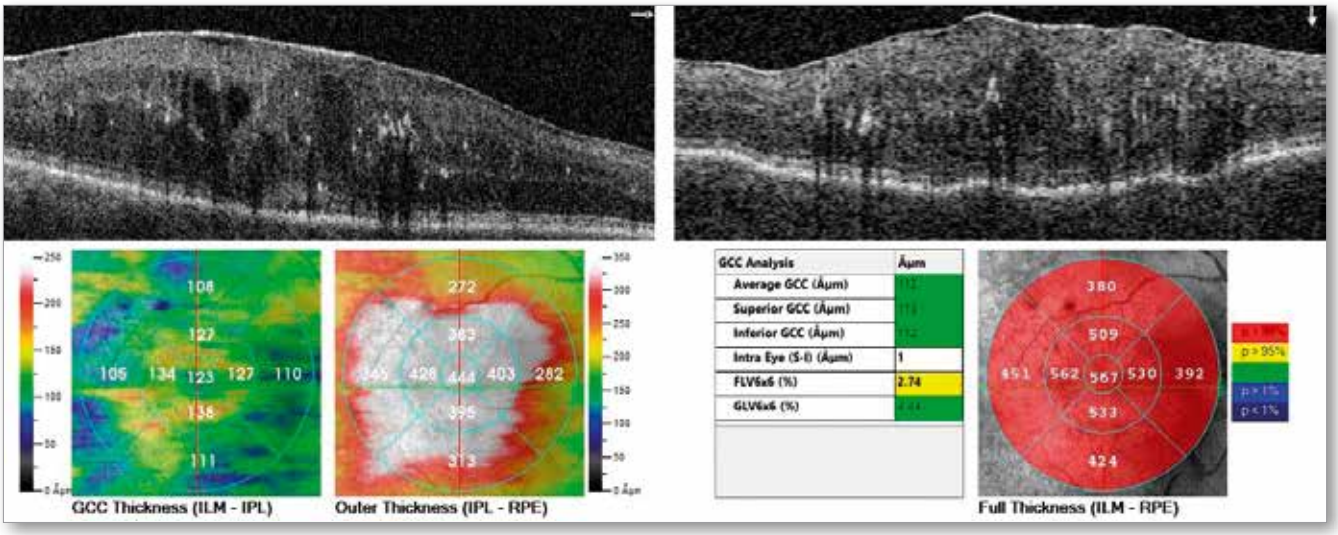

Fig. 1. OCT image of the macula of patient 1 before starting therapy.

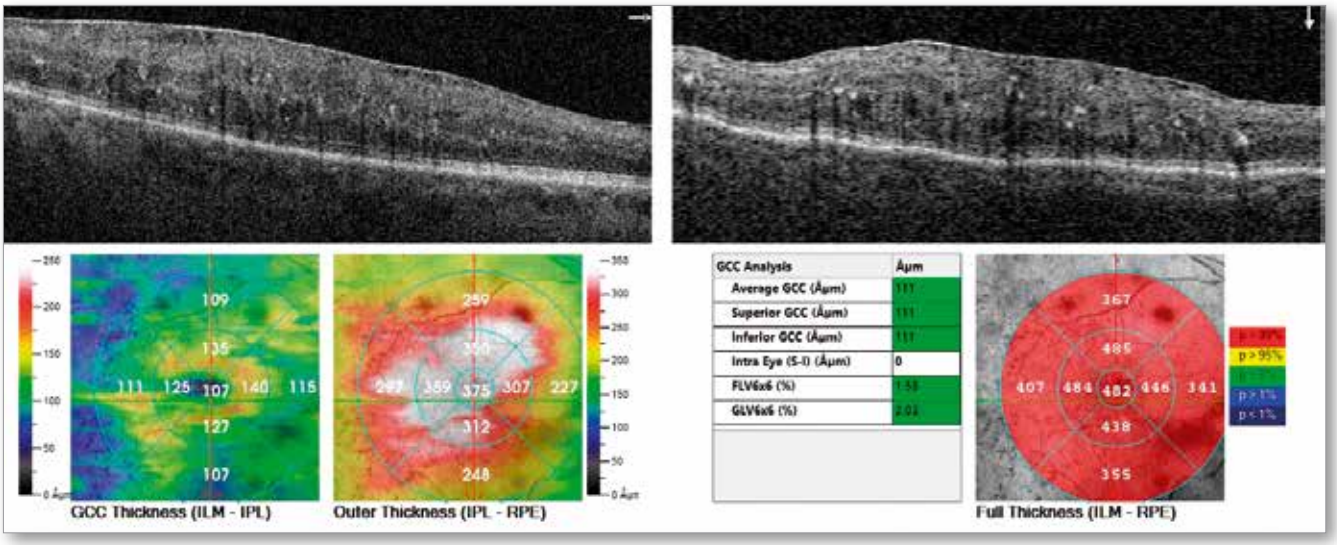

Fig. 2. OCT image of the macula of patient 1 after the first injection of bevacizumab.

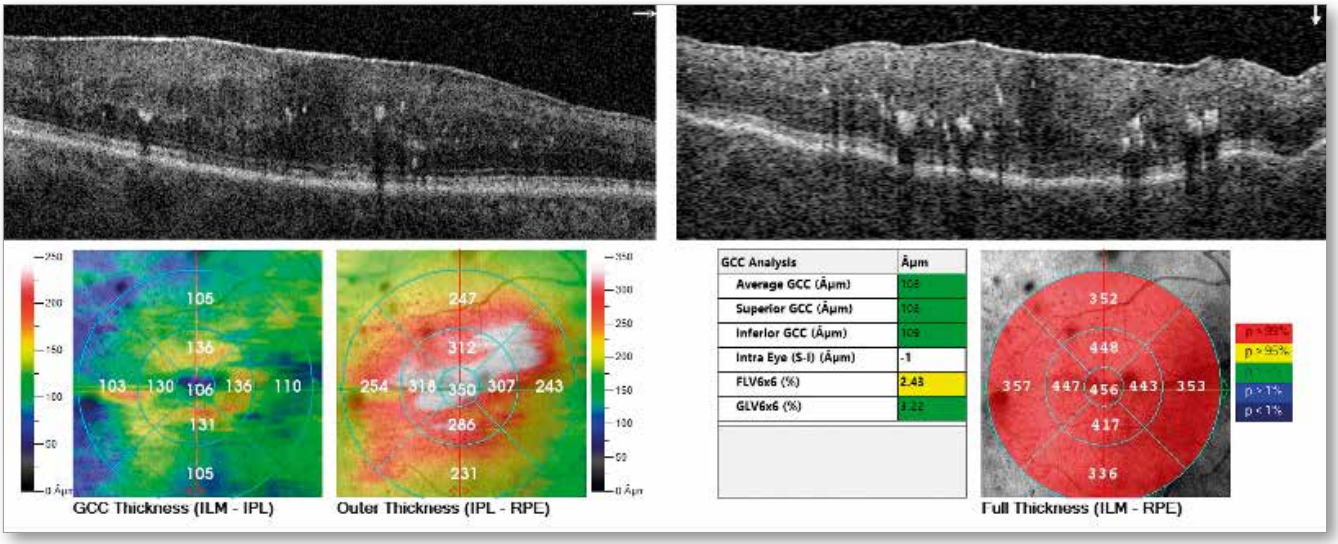

Fig. 3. OCT image of the macula of patient 1 after the second injection of bevacizumab.

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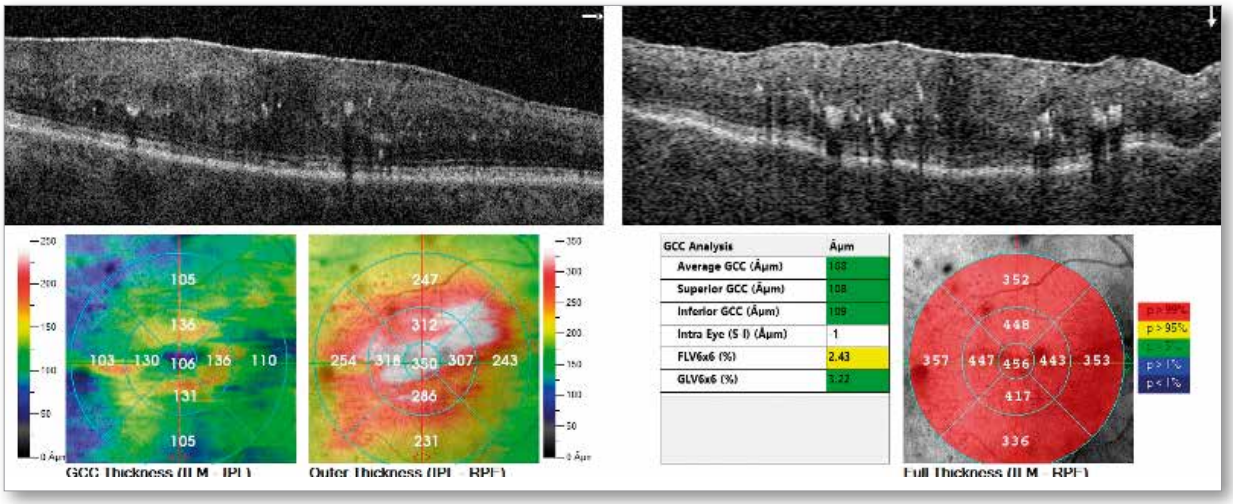

Fig. 4. OCT image of the macula of patient 1 after the third injection of bevacizumab.

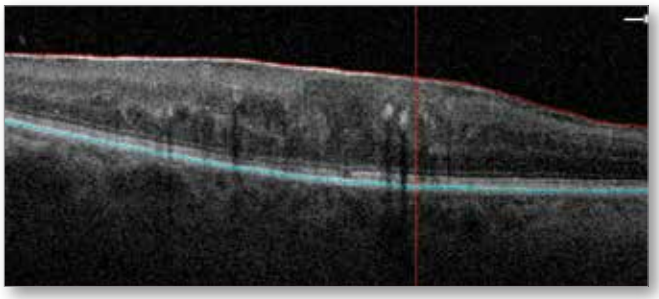

Fig. 5. OCT image of the macula of patient 1 after the fifth injection of bevacizumab.

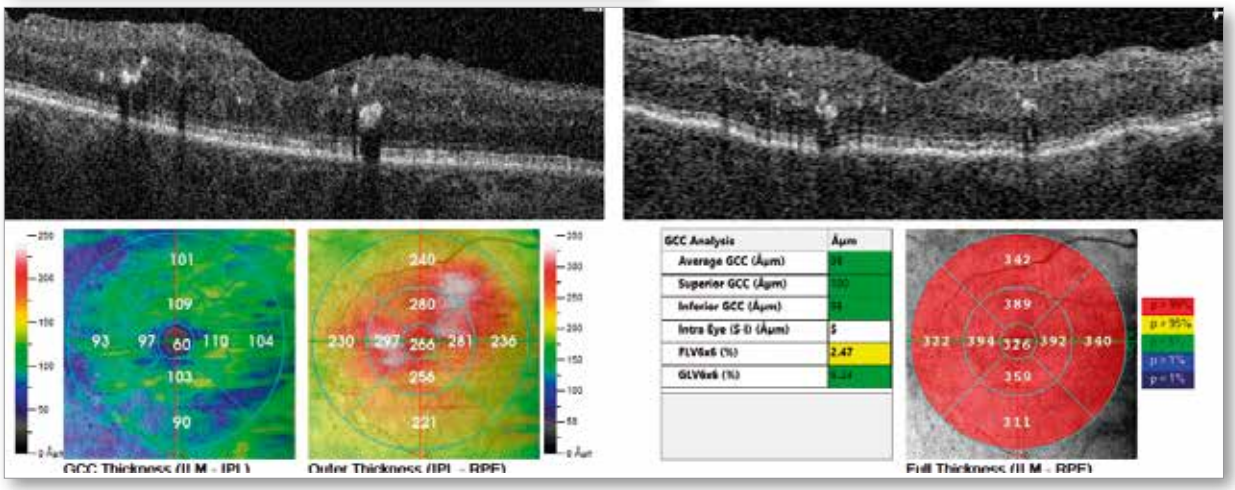

Fig. 6. OCT image of the macula of patient 1 after vitrectomy with macular peeling.

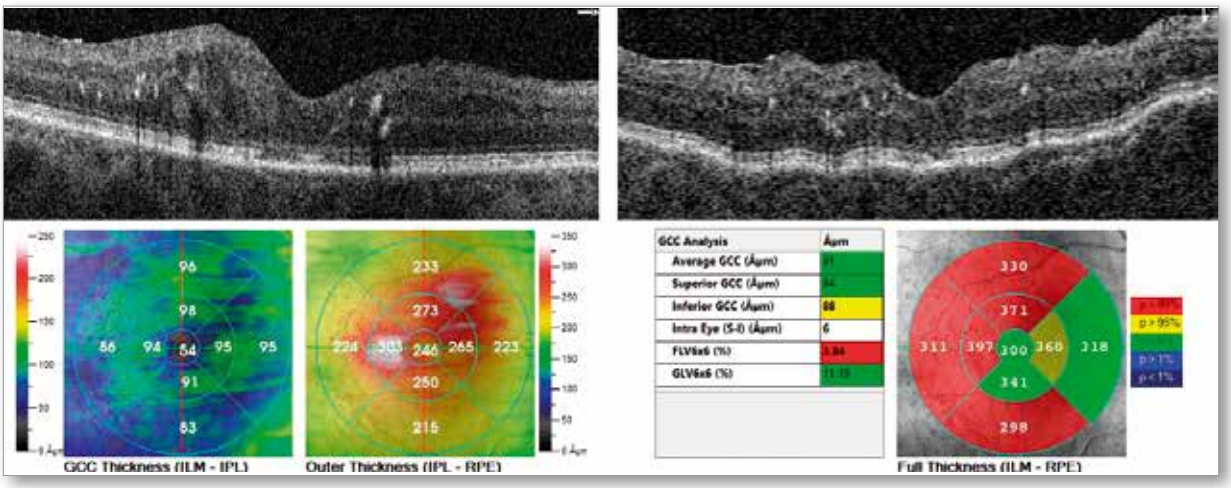

Fig. 7. OCT image of the macula of patient 1 after the first faricimab injection.

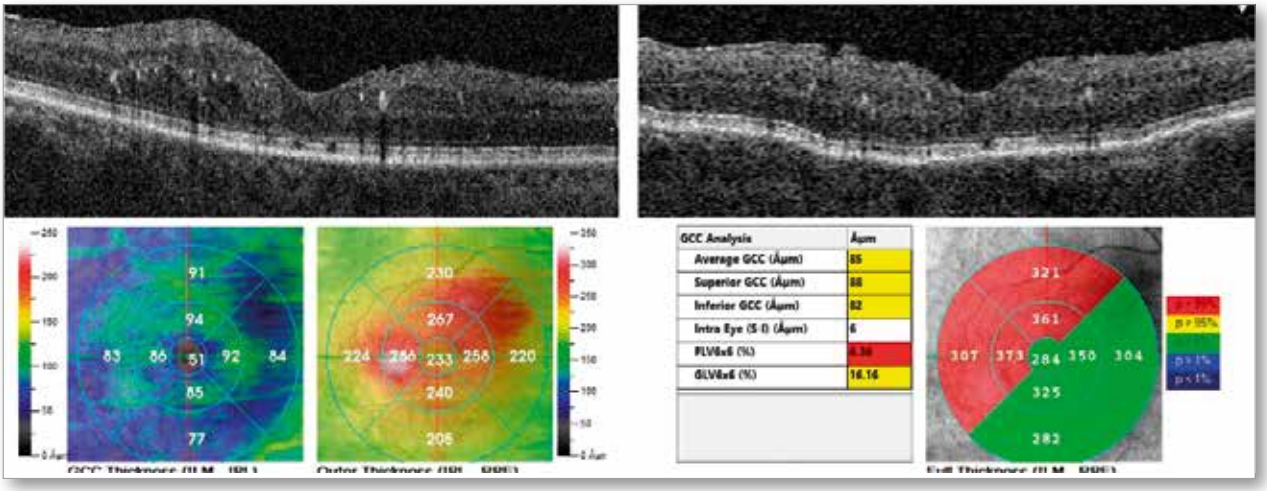

Fig. 8. OCT image of the macula of patient 1 after the second injection of faricimab.

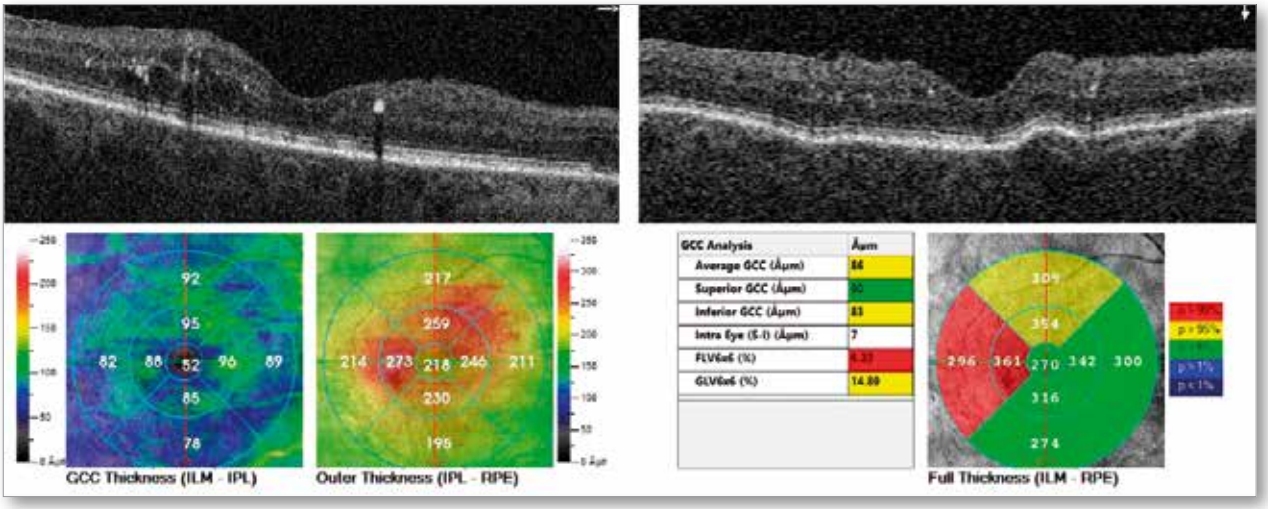

Fig. 9. OCT image of the macula of patient 1 after the third injection of faricimab.

Patient 2

A 57-year-old male patient was scheduled for treatment of diabetic macular edema. At the start of therapy, his BCVA was 0.4, with a central retinal thickness of 473 µm (Fig. 10). The patient's diabetes was well controlled (HbA1c = 6.1 mg%). The presence of ERM was observed. A series of five intravitreal bevacizumab injections was administered (Fig. 10–13). After the injections, BCVA decreased to 0.3 and CRT remained unchanged. A decision was made to proceed with surgical treatment, and a 25G vitrectomy with epiretinal membrane peeling was performed. Postoperatively, the edema nearly completely resolved (Fig. 14). The patient subsequently received a series of intravitreal aflibercept injections at a dose of 2 mg, resulting in improvement of BCVA to 0.5 and a reduction in CRT to 271 µm (Fig. 15).

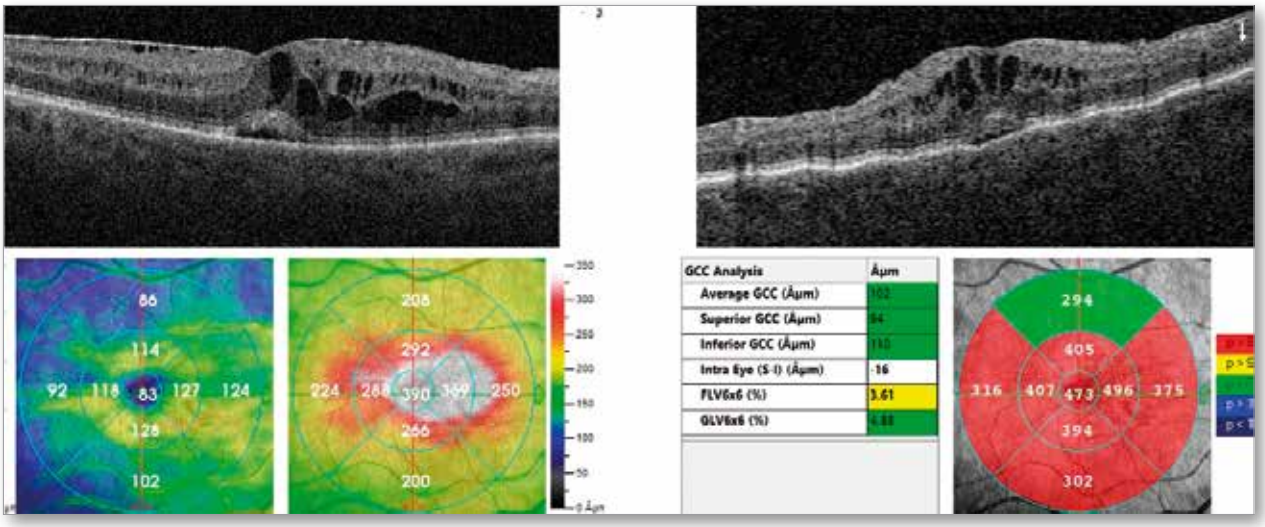

Fig. 10. OCT image of the macula of patient 2 before starting therapy.

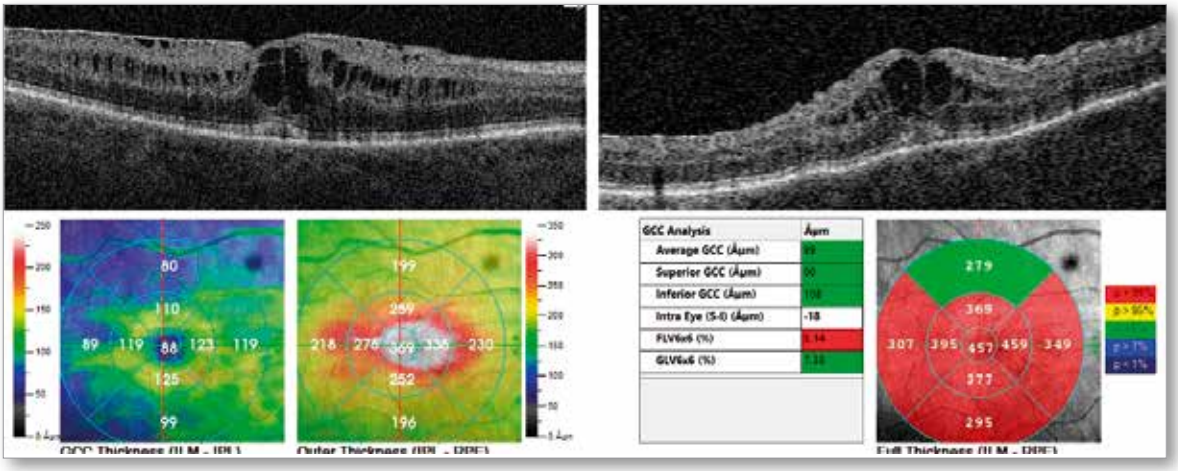

Fig. 11. OCT image of the macula of patient 2 after the first injection of bevacizumab.

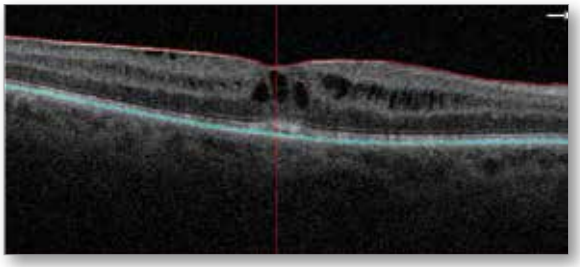

Fig. 12. OCT image of the macula of patient 2 after the third injection of bevacizumab.

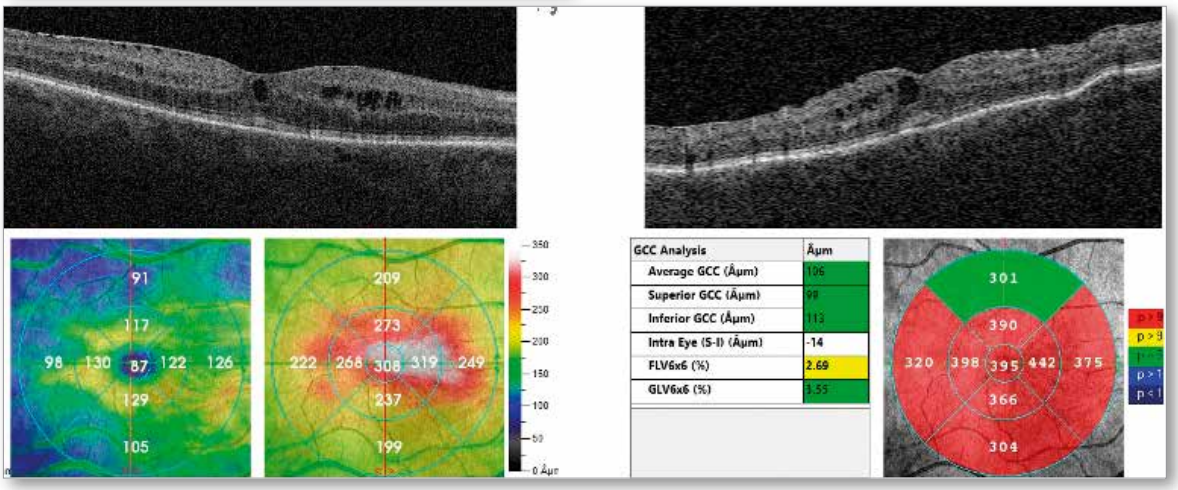

Fig. 13. OCT image of the macula of patient 2 after a series of 5 bevacizumab injections.

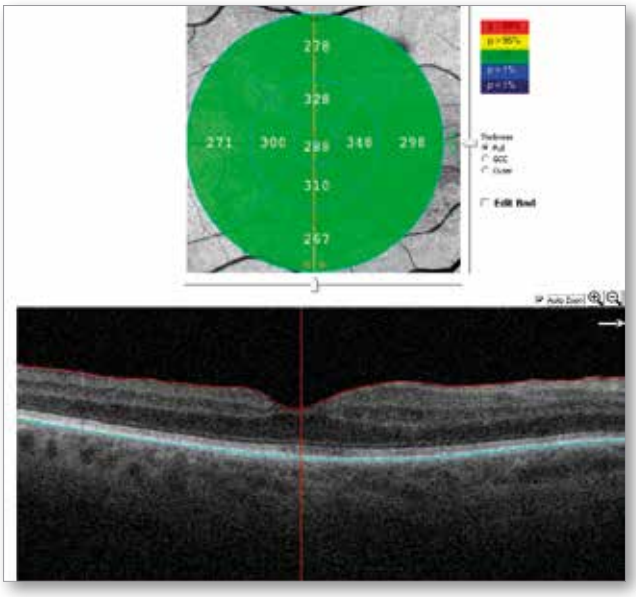

Fig. 14. OCT image of the macula of patient 2 after vitrectomy with macular peeling.

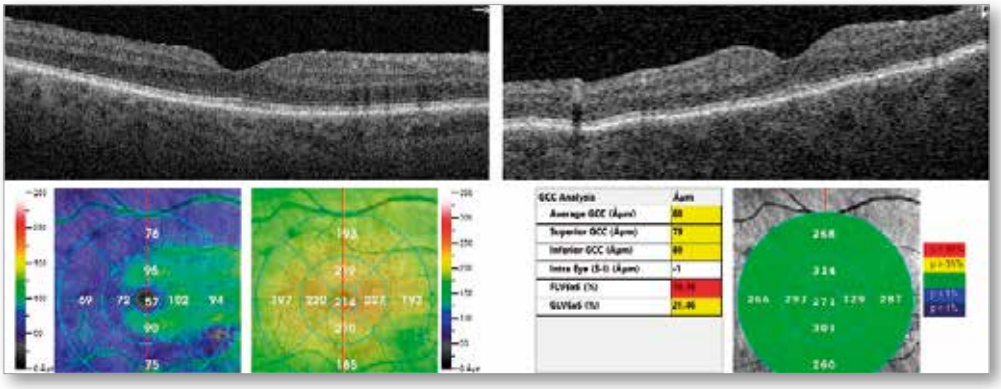

Fig. 15. OOCT image of the macula of patient 2 after vitrectomy with macular peeling and a series of aflibercept injections.

Epiretinal membrane in patients with exudative age-related macular degeneration

It is estimated that approximately 20–30% of patients with exudative age-related macular degeneration (AMD) do not respond to anti-VEGF therapy. One of the most common causes of non-response to therapy is ERM or vitreomacular traction [7]. It is thought that the effectiveness of treatment after vitrectomy with macular peeling may improve due to:

- release of tractional forces on the internal limiting membrane, which suppresses the secretion of pro-inflammatory factors by Müller cells,
- removal of the vitreous body, which may improve the diffusion of VEGF and other cytokines between the retina and the vitreous body,
- increase in intraocular oxygen concentration, which suppresses VEGF production.

Chronic traction is thought to potentially cause degeneration of retinal pigment epithelium (RPE) cells or Bruch's membrane, stimulate inflammation, which may induce or promote the progression of neovascular age-related macular degeneration (nAMD).

In their studies, Luttrull and Spink [8] demonstrated that vitrectomy with ERM peeling may improve visual acuity in selected patients following the loading phase of anti-VEGF therapy.

It should be remembered, however, that removal of the vitreous body may increase clearance and lower the concentration of anti-VEGF agents, which can necessitate more frequent injections after surgery [9].

Patient 3

A 63-year-old woman was diagnosed with active exudative AMD coexisting with ERM. At the initiation of treatment, her BCVA was 0.4 and CRT was 415 μm (Fig. 16). A series of intravitreal brolucizumab injections was administered. After the loading phase, BCVA decreased to 0.2, and CRT remained unchanged (Fig. 16–19). The patient was scheduled for vitrectomy with macular peeling. Following the procedure, disease activity subsided and BCVA improved to 0.4 (Fig. 20–21). Anti-VEGF therapy with brolucizumab was then continued in a 12-week Treat & Extend (T&E) regimen.

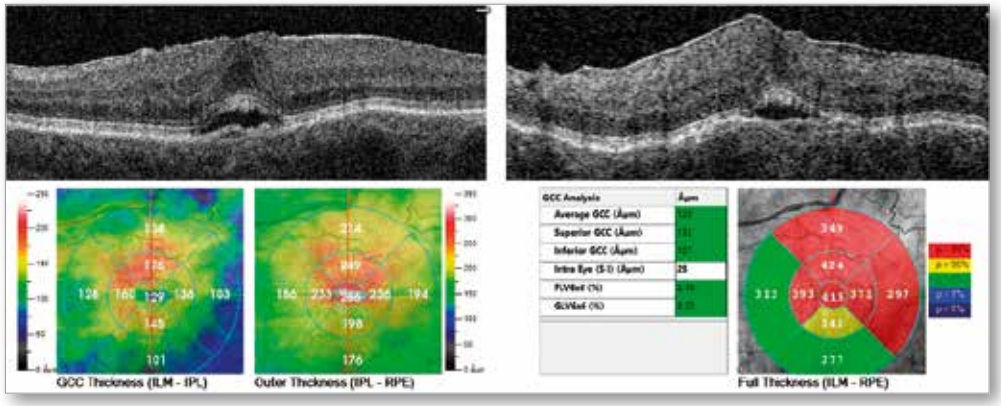

Fig. 16. OCT image of the macula of patient 3 before starting therapy.

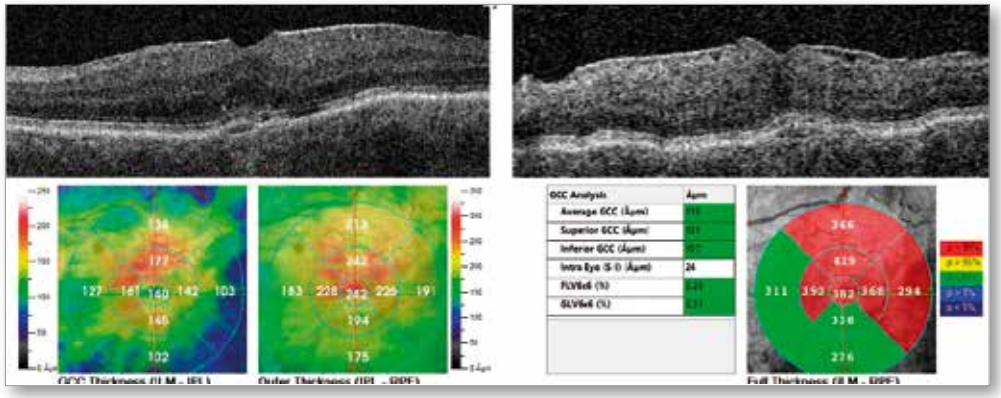

Fig. 17. OCT image of the macula of patient 3 after the first injection of brolucizumab.

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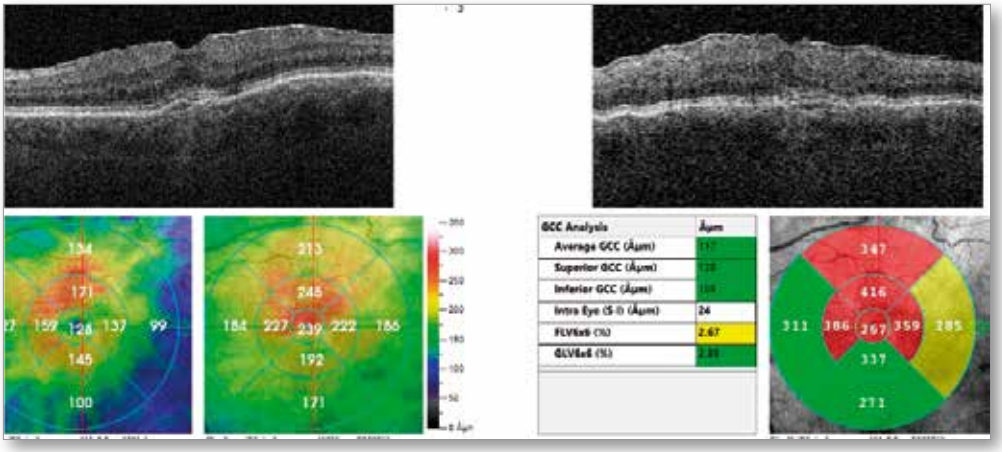

Fig. 18. OCT image of the macula of patient 3 after the second injection of brolucizumab.

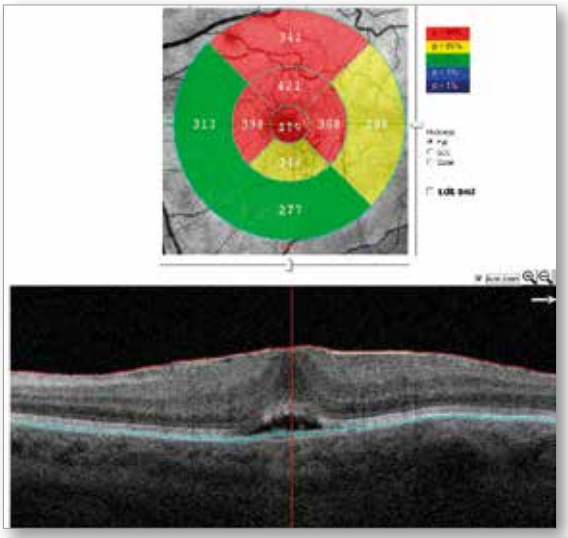

Fig. 19. OCT image of the macula of patient 3 after a series of three brolucizumab injections.

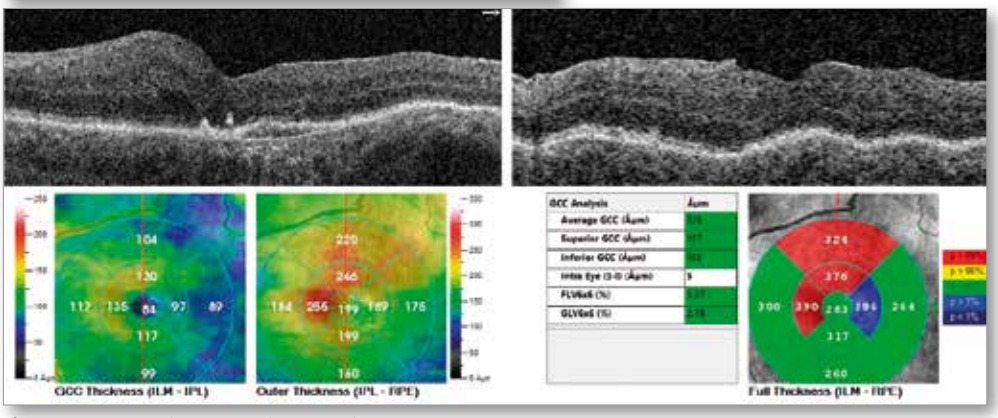

Fig. 20. OCT image of the macula of patient 3 after vitrectomy with macular peeling.

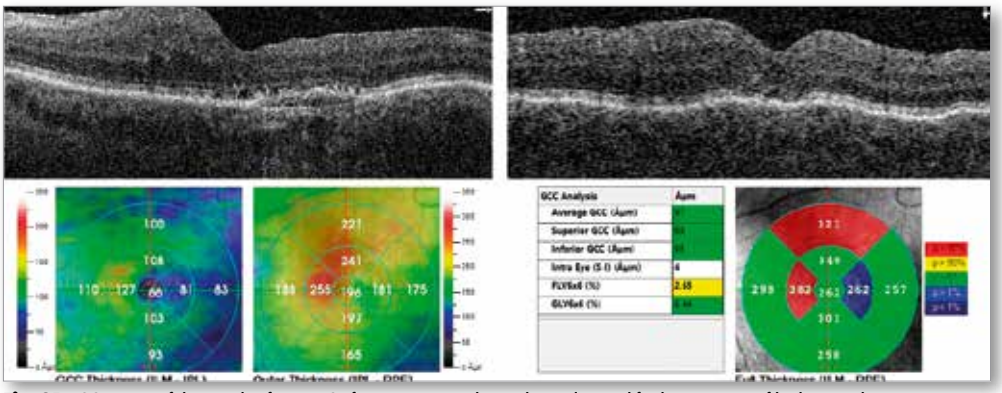

Fig. 21. OCT image of the macula of patient 3 after vitrectomy with macular peeling and further injections of brolucizumab.

Patient 4

A 56-year-old woman had been treated for nAMD for several years. Initially, she received ranibizumab (Fig. 22), followed by a switch to aflibercept at a dose of 2 mg (Fig. 23–25). Persistent disease activity in the form of subretinal fluid was observed despite long-term therapy with injections administered at four-week intervals. With BCVA of 0.5 and CRT of 510 μm, the patient was scheduled for vitrectomy with ERM peeling. Following the surgical intervention, visual acuity initially improved, but high activity of nAMD persisted (Fig. 26–27). A decision was made to switch therapy to faricimab. After a further seven injections, high disease activity persisted and BCVA declined to 0.2. A switch was made to aflibercept 8 mg (Fig. 28–30). Although initial improvement was noted during the loading phase, visual acuity did not improve and disease activity has remained high. The patient continues to be treated with aflibercept 8 mg in a T&E regimen at eight-week intervals (Fig. 31).

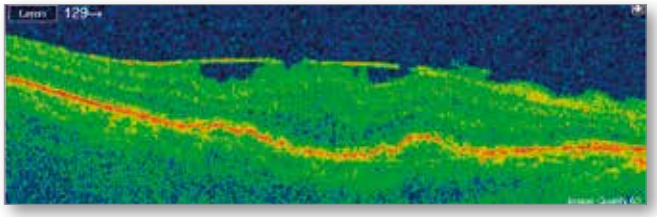

Fig. 22. OCT image of the macula of patient 4 after a series of ranibizumab injections.

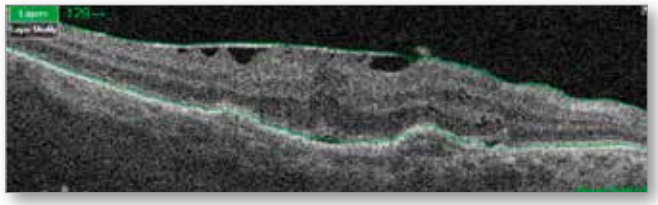

Fig. 23. OCT image of the macula of patient 4 after the first injection of aflibercept 2 mg.

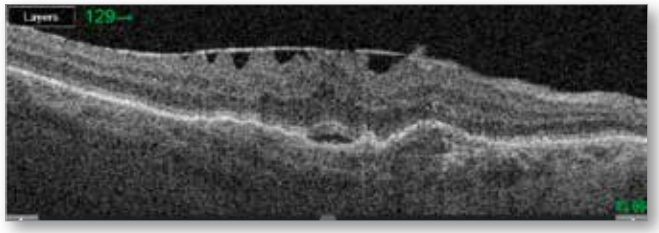

Fig. 24. OCT image of the macula of patient 4 after another injection of 2 mg aflibercept.

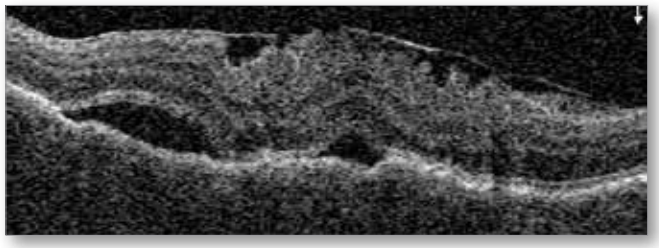

Fig. 25. OCT image of the macula of patient 4 after a series of 2 mg aflibercept injections.

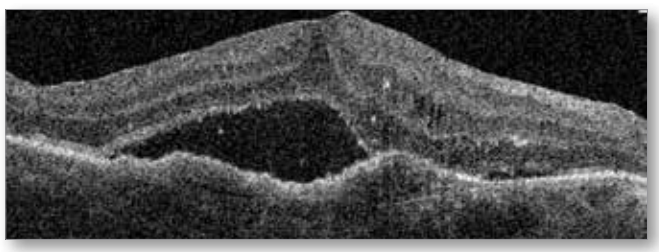

Fig. 26. OCT image of the macula of patient 4 after vitrectomy with macular peeling.

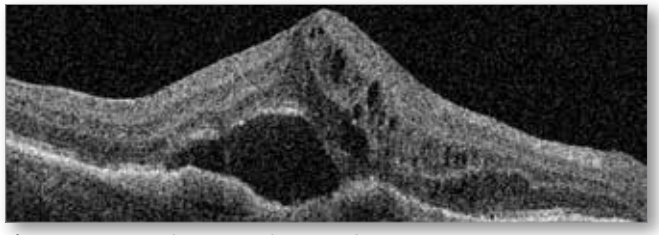

Fig. 27. OCT image of the macula of patient 4 after vitrectomy with macular peeling and further therapy with aflibercept at a dose of 2 mg.

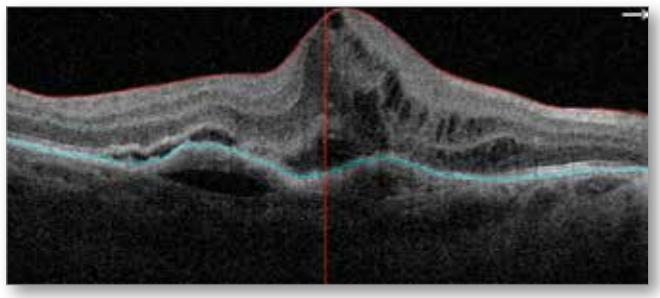

Fig. 28. OCT image of the macula of patient 4 after the first injection of aflibercept 8 mg.

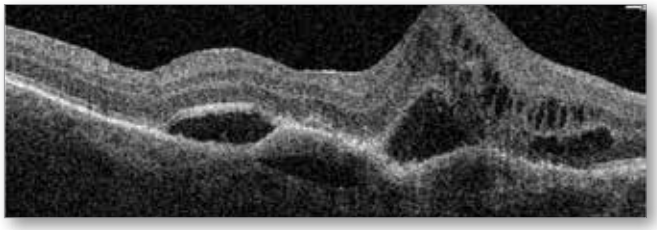

Fig. 29. OCT image of the macula of patient 4 after the second injection of aflibercept 8 mg.

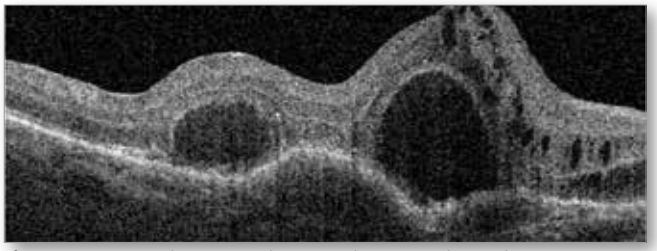

Fig. 30. OCT image of the macula of patient 4 after a series of 8 mg aflibercept injections.

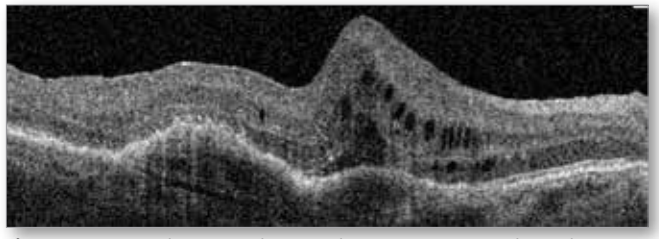

Fig. 31. OCT image of the macula of patient 4 after subsequent injections of 8 mg aflibercept.

Conclusions

In patients with nAMD or DME accompanied by an epiretinal membrane, the decision to proceed with surgical treatment must be carefully considered. It should be noted that, not infrequently, anatomical improvement is not accompanied by corresponding gains in visual function after surgery. With the availability of newer, more potent anti-VEGF agents, a modification of anti-VEGF therapy should be attempted before considering surgical intervention. Vitrectomy should be performed no earlier than after the pharmacological loading phase, and optimally after a longer period of treatment if disease activity persists despite intensive anti-angiogenic therapy.

Disclosure
Conflict of interests: none declared
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Ethics approval: Not applicable.

References:

1. Kanukollu VM, Agarwal P: *Epiretinal Membrane*. [Updated 2023 Jul 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560703/
2. Fraser-Bell S, Guzowski M, Rochtchina E, et al.: *Five-year cumulative incidence and progression of epiretinal membranes: the Blue Mountains Eye Study*. Ophthalmology. 2003 Jan; 110(1): 34– 40. [PubMed]
3. Namba R, Kaneko H, Suzumura A, et al.: *In Vitro Epiretinal Membrane Model and Antibody Permeability: Relationship With Anti-VEGF Resistance in Diabetic Macular Edema.* Invest Ophthalmol Vis Sci. 2019 Jul 1; 60(8): 2942– 2949. doi: 10.1167/iovs.19-26788. PMID: 31284311.
4. Lee SJ, Koh HJ: *Effects of vitreomacular adhesion on anti- vascular endothelial growth factor treatment for exudative age-related macular degeneration.* Ophthalmology. 2011; 118: 101–110.
5. Christoforidis JB, Xie Z, Jiang A, et al.: *Serum levels of intravitreal bevacizumab after vitrectomy, lensectomy and non-surgical controls.* Curr Eye Res. 2013; 38: 761–766.
6. Schechet SA, Devience E, Thompson JT: *The effect of internal limiting membrane peeling on idiopathic epiretinal membrane surgery, with a review of the literature*. Retina. 2017; 37(5): 87380. https://doi.org/10.1097/IAE.0000000000001263
7. 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: 218–227.
8. Lee SJ, Koh HJ: *Effects of vitreomacular adhesion on anti-vascular endothelial growth factor treatment for exudative age-related macular degeneration*. Ophthalmology. 2011; 118: 101–110.
9. Kimura S, Morizane Y, Toshima S, et al.: *Efficacy of vitrectomy and inner limiting membrane peeling in age-related macular degeneration resistant to anti-vascular endothelial growth factor therapy, with vitreomacular traction or epiretinal membrane*. Graefes Arch Clin Exp Ophthalmol. 2016; 254: 1731–1736.

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