

## Anti-vascular endothelial growth factors and cystoid macular edema after cataract surgery: When to use – case study

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Refractory PCME is a rare, but serious vision-threatening complication of cataract surgery. For this reason, this complication has to be managed timely and adequate. Non-steroidal and steroidal anti-inflammatory and anti-VEGF agents like bevacizumab are useful for refractory PCME. OCT has an important role in detecting PCME and measuring central macular thickness to control the treatment of PCME. In this case study, a patient is described after routine uncomplicated PACO surgery with refractory PCME at postop 4<sup>th</sup> week. Despite using topical NSAID+steroidal anti-inflammatory treatment there was no improvement in poor vision and CMT remained stable increased (811  $\mu\text{m}$ ). The vision was increased only after 2 weeks of i.v. bevacizumab injection, macular edema resolved and CMT decreased (280  $\mu\text{m}$ ) which was revealed by OCT. In conclusion, OCT-guided i.v. bevacizumab is a safe and well-tolerated therapeutic option for refractory PCME.

**Keywords:** Intra-vitreous bevacizumab, OCT, cataract surgery, cystoid macular edema

### INTRODUCTION

Pseudophakic cystoid macular edema (PCME) is one of the vision-threatening complications after cataract surgery (Copete et al., 2019). PKME, also known as Irvine-Gass syndrome, was first described in 1953 by S.R.Irvine (Irvine, 1953) and later by D.Gass (Gass, 1966). In general, as in cystoid macular edema (CME), PCME is a result of the accumulation of retinal fluid between the inner and outer nuclear layers of the retina and the formation of fluid-filled cystic spaces (Kanski, 2007).

The incidence of PCM varies from 1 to 30% (depending on factors such as surgical methods, intraoperative complications, surgeon's experience, presence of concomitant risk factors, etc.) (Copete et al., 2019; Grzybowski et al., 2016; Kodjikian et al., 2017). In the absence of risk factors and intraoperative complications, 1-2% (Grzybowski et al., 2016) are found. PCME after phacoemulsification of the cataract (PACO)

is less frequent compared to extracapsular cataract extraction (ECCE) and especially intracapsular extraction (Wetzig et al., 1979; Powe et al., 1994; Montes et al., 2003). Modern imaging methods such as Fundus Fluorescein Angiography (FFA) and Optical Coherence Tomography (OCT) and medical treatment (non-steroidal and anti-steroidal anti-inflammatory) have a special role in early detection, effective targeting and treatment of PCME (Kodjikian et al., 2017; Guo et al., 2015; Wittpenn et al., 2008; Ching et al., 2006). However, refractory CME remains on the agenda as it is difficult to respond to traditional treatment. Recently, it has been shown that anti-VEGF drugs are more effective in the treatment of refractory PCME than oral, subtenon and intravitreal (i/v) administrations of non-steroidal and steroidal anti-inflammatory drugs (Arevalo et al., 2009; Barone et al., 2009; Demirel et al., 2012; Akay et al., 2020; Spitzer et al., 2008). Measuring the central macular thickness (CMT) with OCT is a very important step in evaluating and guiding the effectiveness of treatment (Ching et al., 2006).

The aim of this work was to evaluate the clinical efficacy, safety and timing of i/v bevacizumab guided by OCT in the treatment of refractory PCM after uncomplicated PACO.

## MATERIALS AND METHODS

Clinical case: a patient with type 2 diabetes a long time visited our clinic with a complaint of poor vision in both eyes; initial diagnosis - cataract of both eyes.

During examination:

Vis OD=0.2 n/cor, Tn OD=16 mm.Hg.

Vis OS=0.04 n/cor, Tn OD=18 mm.Hg.

In both eyes, the fundus is not examined in detail. Due to the poor dilation of the pupil, diclofenac sodium was prescribed to the eye to be operated on, 1 drop 3 times a day for 3 days before surgery. FACO + intraocular lens implantation (IOL) surgery was performed in the patient's left eye. The operation and the postoperative (postop) period were uneventful.

Postop Day 1:

Vis OS=0.8, Tn OS=17 mm Hg

The cornea is transparent, the anterior chamber fluid is clear, and the pupil is alive.

Treatment: prednisolone acetate - 1 drop 6 times, moxifloxacin - 1 drop 6 times, diclofenac sodium - 1 drop 3 times.

Postop 3rd week:

Visual functions are fixed, fixed drops have been reduced.

However, in the 4<sup>th</sup> postoperative week, the patient returned with a complaint of a serious decrease in vision in the left eye.

During examination:

Vis OD=0.08 n/corrected, Tn OS=20 mm.Hg

The cornea is transparent, the anterior chamber fluid is clear, the vitreous is stable (US), the pupil's reaction to light is alive, the IOL is in a stable position inside the capsule bag.

Fundus examination: significant macular edema and loss of foveal reflex are noted.

OCT: intraretinal cysts, subretinal fluid accumulation and increased CMT (811  $\mu$ m) are noted (Fig. 1 and 2).

Prednisolone acetate - 1 drop 6 times, nepafenac - 1 drop - 4 times, oral diacarb 1 tab (0.5 mg) 1 time per day for 5 days, subtenon

triamcinolone acetate (0.5 mL) was injected.

2 weeks later: the vision in the left eye has improved slightly.

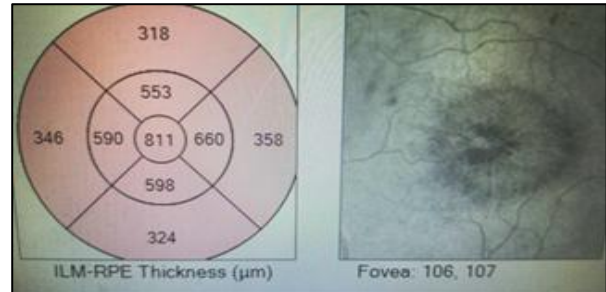


Fig. 1. OCT shows a prominent increase of CMT (811  $\mu$ m) due to the accumulation of subretinal fluid

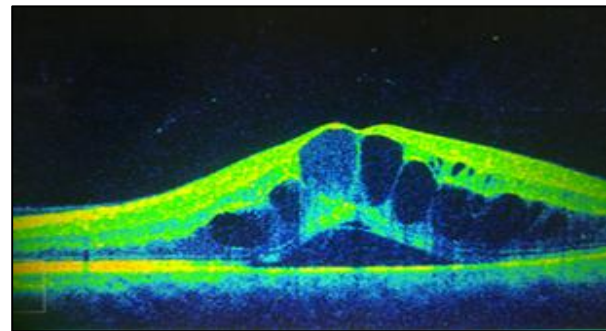


Fig. 2. OCT: Multiple fluid-filled intraretinal cystic spaces typical of PCME

Vis OS=0.2 n/cor, Tn OS=19 mm.Hg

However, since there was no significant change in CMT, close follow-up of the treatment was continued. Postop 8<sup>th</sup> week: visual acuity did not change and did not differ from the 6<sup>th</sup> week.

OCT - CMT slightly decreased (680 $\mu$ m), (Fig. 3 and 4). Bevacizumab (1.25 mg) was injected i.v. into the left eye.

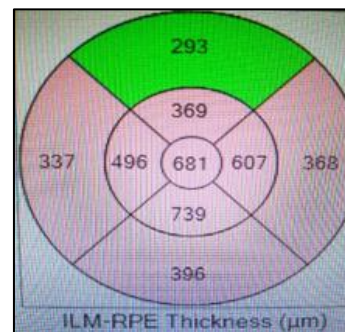
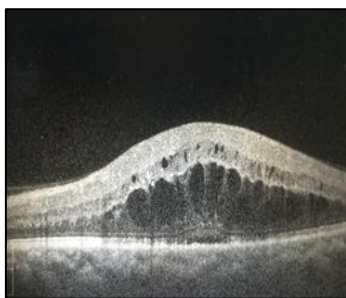


Fig. 3. OCT-postop 8th week: CMT continues to remain decreased (680 $\mu$ m)

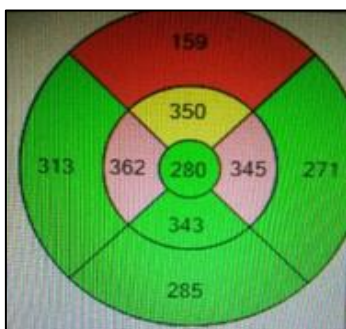


**Fig. 4.** OCT-postop 8th week: cystic spaces remain

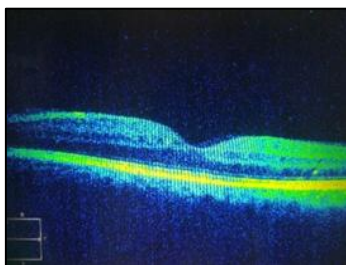
2 weeks after the injection:

Vis OS=0.7 n/cor, Tn OS=17 mm.Hg

OCT - CMT significantly decreased (280  $\mu$ m) (Fig. 5 and 6).



**Fig. 5.** 2 weeks after i/v injection: OCT confirms a significant reduction in CMT thickness



**Fig. 6.** 2 weeks after the injection: OCT shows the absorption of intraretinal fluid and loss of cystic spaces

Nepafenac was continued with 1 drop 3 times a day.

Postop 12<sup>th</sup> week:

Vis OS=0.9, Tn OS=16 mm.Hg, foveal reflex is clear, Amsler test-negative.

## RESULTS AND DISCUSSION

Irvine-Gass syndrome or PCME causes cystoid edema in the macula after cataract

surgery, causing vision loss (Copete et al., 2019; Sonmez et al., 2007). Although PCME can occur after uncomplicated cataract surgery (Grzybowski et al., 2016), more commonly PCME (especially refractory PCME) develops after complicated surgery due to anterior vitreous displacement and vitreous loss during surgery (Schepens et al., 1984), posterior capsule tear (Onal et al., 2004), and inflammation caused by contact of the IOL with the iris (Zaczek et al., 1998). It is thought that the disruption of internal and external blood-retinal barriers or the activation of the inflammatory cascade in all structures of the eye as a result of the inflammation caused by the increase of prostaglandins due to surgical trauma has an important role in the development of PCME (Xu et al., 2011; Zur et al., 2017). On the other hand, it is thought that the increase in metabolic activity in the RPE due to the effect of light entering into the eye during surgery leads to activation of the angiogenesis, which can lead to the development of PCME (Ueta et al., 2012). Factors such as diabetes, uveitis, epiretinal membrane (ERM), use of prostaglandin analogues, choroidal tumors and aging are known to play a role in the development of PCME also (Arcieri E.S. et al., 2005). Due to the high metabolic activity of the fovea, the mentioned pathological changes create the basis for the development of CME in the foveal zone, which in turn leads to an increase in CME and a decrease in visual acuity (Nagpal et al., 2001).

It should be noted that opinions on the treatment of PCME are controversial: although self-regression of PCME is possible in many cases, treatment is very important in other cases, especially in refractory PCME (Kodjikian et al., 2017). There is strong evidence of the effectiveness of anti-VEGFs along with non-steroidal and steroidal anti-inflammatory drugs in the treatment of refractory CME (Kodjikian et al., 2017; Kessel et al., 2014; Mitropoulos et al., 2015, Lin et al., 2018).

In the patient we report, refractory PCME was detected in the 4<sup>th</sup> postoperative week. In addition to a serious decrease in visual acuity, the loss of the foveal reflex, a prominent increase in the CMT in the OCT examination, and the appearance of fluid-filled cystic spaces between the layers of the retina, the typical clover leaf sign

(Rishi et al., 2013, Fig.7) in the FFA confirm Irvine-Gass syndrome.



**Fig. 7.** The clover leaf sign in FFA confirms the presence of fluid-filled cystic spaces between the layers of the retina

It should also be noted that the patient has long-term diabetes mellitus as a risk factor. Although the patient was given subtenon triamcinolone acetate injection and oral carbonic anhydrase inhibitor along with topical non-steroid and steroid drops, the visual acuity improved slightly, but the OCT image at week 8 postop was not encouraging: no decrease in CMT was noted. Prolonged elevation of CMT despite of treatment posed a serious threat to visual acuity as an indicator of refractory PCM. In order to eliminate this threat, as shown in the scientific literature (Kodjikian L. et al., 2017, Arevalo J.F. et al., 2009, Barone A. et al., 2009, Demirel S. et al., 2012), intravitreal bevacizumab was injected. 2 weeks after the injection, an increase in visual acuity to 0.7 was noted. Here we should especially mention the role of OCT. Thus, OCT is a method that allows clinical monitoring of macular edema by measuring macular thickness and detecting intraretinal cysts (Guo S. et al., 2015). Therefore, the correct decision - intravitreal bevacizumab injection - was made because OCT showed no decrease in CCT despite a subjective improvement in vision at the 8<sup>th</sup> week postoperatively.

Continued observation showed the complete recovery of the patient's visual acuity and foveal reflex, regression of the CCT to its normal size, absorption of macular edema.

## CONCLUSION

In conclusion, we should note that refractory PCMO is a serious vision-threatening complication that develops after cataract surgery. OCT-guided intravitreal bevacizumab injection in eliminating this complication resistant to medical treatment is effective and safe, leading to significant improvement of visual acuity, reduction of CMT, and absorption of macular edema.

## REFERENCES

- Akay F., Işik M.U., Akmaz B., Güven Y.Z.** (2020) Comparison of intravitreal anti-vascular endothelial growth factor agents and treatment results in Irvine-Gass syndrome. *Int. J. Ophthalmology*, **13(10)**: 1586-1591.
- Arcieri E.S., Santana A., Rocha F.N. et al.** (2005) Blood-aqueous barrier changes after the use of prostaglandin analogues in patients with pseudophakia and aphakia: a 6-month randomized trial. *Arch.Ophthalmol.*, **123**: 186-192.
- Arevalo J.F., Maia M., Garcia-Amaris M.A., Roca J.A., Sanchez J.G., Berrocal M.H., Wu L.**(2009) Pan-American Collaborative Retina Study Group intravitreal bevacizumab for refractory pseudophakic cystoid macular edema, the Pan-American Collaborative Retina Study Group results. *Ophthalmology.*, **116 (8)**: 1481-1487.
- Barone A., Russo V., Prascina F., Delle Noci N.** (2009) Short-term safety and efficacy of intravitreal bevacizumab for pseudophakic cystoid macular edema. *Retina*, **29 (1)**: 33-37.
- Ching H.Y, Wong A.C., Wong C.C., Woo D.C., Chan C.W.** (2006) Cystoid macular edema and changes in retinal thickness after phacoemulsification with optical coherence tomography. *Eye (London)*, **20 (3)**: 297-303.
- Copete S., Marti-Rodrigo P., Muniz-Vidal R., Pastor-Idolarte S., Rigo J., Figueroa M.S., Garcia-Arumi J., Zapata M.A.** (2019) Preoperative vitreoretinal interface abnormalities on spectral domain optical coherence tomography as risk factor for pseudophakic cystoid macular edema after



- phacoemulsification. *Retina*, **39(11)**: 2225-2232.
- Demirel S., Batioğlu F., Özmert E.** (2012) Intravitreal ranibizumab for the treatment of cystoid macular edema in Irvine-Gass syndrome. *J. Ocular Phamacol. Ther.*, **28 (6)**: 636-639.
- Gass J.D., Norton E.W.** (1966) Cystoid macular edema and papilledema following cataract extraction. A fluorescein fundoscopic and angiographic study. *Arch. Ophthalmol.*, **76**: 646-666.
- Grzybowski A., Sikorski B.L., Ascaso F.Y., Huerva V.** (2016) Pseudophakic cystoid macular edema update 2016. *Clinical Interventions in Aging*, **11**: 1221-9.
- Guo S., Patel S., Baumrind B., Johnson K., Levinsohn D., Marcus E., Tannen B., Roy M., Bhagat N., Zarbin M.** (2015) Management of pseudophakic cystoid macular edema. *Survey of Ophthalmology*, **60**: 123-37.
- Irvine S.R.** (1953) A newly defined vitreous syndrome following cataract surgery. *Am. J. Ophthalmol.*, **36**: 599-619.
- Kanski J.J.** (2007) *Clinical Ophthalmology. A systematic approach.* 6th Edition. Butterworth Heinemann: 931 p.
- Kessel L., Tendal B., Jorgensen K.J., Erngaard D., Flesner P., Andresen J.L., Hjortdal J.** (2014) Post-cataract prevention of inflammation and macular edema by steroid and nonsteroidal anti-inflammatory eye drops: a systematic review. *Ophthalmology*, **121**: 1915-1924.
- Kodjikian L., Bellocq D., Bodaghi G.** (2017) Management of Irvine-Gass syndrome. *J. Français D Ophthalmologie*, **40 (9)**: 788-792.
- Lin C.J., Tsai Y.Y.** (2018) Use of aflibercept for the management of refractory pseudophakic macular edema in Irvine-Gass syndrome and literature review. *Retinal Cases and Brief Reports*, **12(1)**: 59-62
- Mentes J., Erakgun T., Afrashi F.** (2003) Incidence of cystoid macular edema after uncomplicated phacoemulsification. *Ophthalmologica*, **217**: 408-412.
- Mitropoulos P.G., Chatziralli İ.P., Peponis V.G., Drakos E., Parikakis E.A.** (2015) Intravitreal ranibizumab for the treatment of Irvine-Gass syndrome. *Ocular immunology and inflammation*. **23**: 225-231.
- Nagpal M., Nagpal K., Nagpal P.N.** (2001) Postcataract cystoid macular edema. *Ophthalmol. Clin. North Am.*, **14**: 651-659.
- Onal S., Gorum N., Gucukoğlu A.** (2004) Visual results and complications of posterior chamber intraocular lens implantation after capsular tear during phacoemulsification. *Ophthalmic Surg. Lasers Imaging*, **35**: 219-224.
- Powe V.R., Schein O.D., Gieser S.C., Tielsch J.M., Luthra R., Javitt J., Steinberg E.P.** (1994) Synthesis of the literature on visual acuity and complications following cataract extraction with intraocular lens implantation. *Cataract Patient Outcome Research Team. Arch Ophthalmol*, **112**: 239-252.
- Rishi P., Rishi E., Sharma T., Bhende M., Sen P., Ratra D., Gopal L.** (2013) *The Sankara Nethralaya Atlas of Fundus Fluorescein Angiography.* 2-nd edition. Jaypee Brothers Medical Publishers (P) Ltd, 606 p.
- Schepens C.L., Avila M.P., Jalkh A.E., Trempe C.L.** (1984) Role of vitreous in cystoid macular edema. *Surv. Ophthalmol.*, **28**: 499-504.
- Sönmez P.A., Atmaca L.S., Özyol E.** (2007) Ön segment cerrahisi sonrası kistoid macula ödemi. Literatür xülassesı (Review). *Ret-Vit.*, **15**: 71-75.
- Spitzer M.S., Ziemssen F., Yoeruek E. et al.** (2008) Efficacy of intravitreal bevacuzimab in treating pseudophakic cystoid macular edema. *J. Cataract Refract. Surgery*, **34(1)**: 70-75.
- Ueta T., Inoue T., Yuda K., Furukawa K., Yanagi Y., Tamaki Y.** (2012) Intence physiological light upregulates vascular endothelial growth factor and enhances choroidal neovascularization via peroxisome proliferator-activated receptor  $\gamma$  coactivator-1a in mice. *Arterioscler. Thromb. Vasc. Biol.*, **32 (6)**: 1366-1371.
- Wetzig P.C., Thatcher D.B., Christiansen J.M.** (1979) The intracapsular versus the extracapsular cataract technique in relationship to retinal problems. *Trans. Am. Ophthalmol. Soc.*, **77**: 339-347.
- Wittpenn J.P., Silverstein S, Heier J., Kenyon K.R., Hunkeler J.D., Earl M., Acular L.S.** (2008) For Cystoid Macular Edema(ACME) Study Group A randomized, masked comparison of topical ketorolac 0.4% plus steroid vs steroid alone in low-risk cataract surgery patients. *Am. J. Ophthalmol.*, **146(4)**: 554-560.
- Xu H.P., Chen M., Forrester J.V., Lois N.**

- (2011) Cataract surgery induces retinal pro-inflammatory gene expression and protein secretion. *Invest. Ophthalmol. Vis. Sci.*, **52(1)**: 249-255.
- Zaczek A., Petrelius A., Zetterstrom C.** (1998) Posterior continuous curvilinear capsulorhexis and postoperative inflammation. *J. Cataract Refract. Surg.*, **24**: 1339-1342.
- Zur D., Loewenstein A.** Postsurgical cystoid macular edema. *Dev. Ophthalmol.*, **58**: 178-190.

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