Long-Term Retinal Thickness Changes in Patients of Non-Resistant Pseudophakic Cystoid Macular Edema

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ABSTRACT

Purpose: We aimed to investigate retinal thickness data in these patients with non-refractory pseudophakic cystoid macular edema.

Materials and Methods: We retrospectively reviewed patients with non-persistent pseudophakic cystoid macular edema who responded to topical therapy plus follow-up within 3 months between January 2018 and October 2020. Age, gender, anterior and posterior segment findings, intraocular pressures, refractive errors and axial lengths of the patients were recorded. Macular layers, volumes and ganglion cell analysis were examined by optical coherence tomography. The distance between the inner limiting membrane and the outer limiting membrane was measured in the inner retinal layer, and it was recorded as M1.

Results: The mean age was 71.33±7.12 in the patients included. Baseline visual acuity was 0.48±0.23 in logMAR in the patient group, while final visual acuity was 0.1±0.096 in logMAR. Average recovery time was 2 months (1-3 months). When the patient and healthy eyes were compared, significant thinning was found in 9 quadrants according to the ETDRS, inner retinal layer (M1), foveal thickness. A strong positive correlation was found between post-treatment vision levels and M1 measurements of eyes with PCME. (p= 0.000)

Conclusion: It should be kept in mind that even if vision is restored in non-resistant cystoid macular edema, it may cause atrophy in the retinal layers.

Keywords: Optical coherence tomography, pseudophakic cystoid macular edema, retinal atrophy.

INTRODUCTION

Pseudophakic cystoid macular edema (PCME), also known as Irvine-Gass syndrome, is defined as macular edema which develops following cataract surgery and leads unexpected loss of vision. It generally develops in cystoid form (Figure 1). Before phacoemulsification era, it was more frequently seen due to disruption in posterior capsule barrier resulting from more aggressive surgical techniques.[1] Although its incidence has been decreased with surgeries using smaller incision upon introduction of phacoemulsification technique, it can be still observed during postoperative period. The disease was first described by R. Irvine in clinical manner; thereafter, it was established using angiography by Gass.[2] Although fundus fluorescein angiography (FFA) have been used more intensively in the diagnosis in the past, the diagnosis has been facilitated by widespread use of optical coherence tomography OCT which plays important role in the follow-up of the patients.[3] Its incidence varies across different studies. In a study including 928 eyes, Irvine-Gass syndrome incidence was found as 9% while it was found as 2-4% in a larger series including 1000 eyes.[4,5] Its physiopathology hasn't been fully elucidated and there is no consensus on its treatment.[6] In the literature, it is tended to define PCME's regressed within 3 months as non-persistent and those persisting ≥¨4 months as chronic.[7] The triggering factors include prolonged surgery, complicated cataract surgery, use of iris retractors, diabetic retinopathy, retinal vein occlusion and vitreoretinal interface anomalies such as epiretinal membrane.[8] In animal studies, it was shown that increased pro-inflammatory cytokines led edema.[9,10] Although widely accepted approach is topical treatment and follow-up over 3 months, intravitreal treatment modalities are used in cases with persistent edema. Topical non-steroid anti-inflammatory drugs (NSAIDs), topical steroids and oral carbonic anhydrase inhibitors can be used as first-line treatment. Therapeutic response is achieved with topical treatment and follow-up in general. In several studies,

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intravitreal injections can be used in resistant cases.[11-13] In this study, it was aimed to investigate long-term functional and anatomic retinal outcomes following topical treatment and follow-up in cases with non-resistant, pseudophakic cystoid macular edema.

MATERIALS AND METHODS

We retrospectively reviewed patients with non-persistent Irvine-Gass syndrome who responded to topical therapy plus follow-up within 3 months Ophthalmology Clinic of Atatürk Training Hospital, İzmir Katip Çelebi University between January 2018 and October 2020. The study was approved by Ethics Committee. The study was conducted in accordance to tenets of Helsinki Declaration. The study included patients with cystoid macular edema who recovered within 3 months without need for intravitreal treatment. Control OCT scans were performed 6 months after diagnosis. Figure 1 shows diffuse cystoid macular edema on retinal image of a patient at postoperative week 2. The patients with spherical equivalent >3 diopter, axial length <21 mm or >24 mm were excluded. Again, the patients with uveitis, retinal disorders (e.g. retinal vein occlusion, diabetic retinopathy, epiretinal membrane) and glaucoma; those using prostaglandin analogs; and those with pseudo-exfoliative syndrome were also excluded. The contralateral normal eyes where no surgery was performed were includes as controls. In all patients, data regarding anterior and posterior segment examination, intraocular pressure values, refractive values, duration of impaired vision and baseline and final visual acuity were recorded. The visual acuity were also recorded as logMAR. All patients underwent optical coherence tomography (OCT) scan and fundus fluorescein angiography (FFA). On OCT, macular measurements, macular volume values and ganglion cell analyses were obtained from 9 quadrants in accordance to ETDRS protocol. In addition, two measurements were performed using OCT. The distance from internal limiting membrane (ILM) to external limiting membrane (ELM) was defined as inner retinal thickness (IRT) and expressed as M1. The distance between ELM and retinal pigment epithelium (RPE) was defined as photoreceptor layer and expressed as M2 (Figure 2). The patient were treated with topical steroid (prednisolone 1%) and non-steroid anti-inflammatory agent (nepafenac 0.1%) during first 3 months. In control visit on month 6, OCT scan was obtained in all patients. M1 and M2 with atrophy were observed (Figure 3). The PCME patients with visual acuity <0.3 logMAR (6/12) on month 3 who were scheduled for anti-VEGF treatment were excluded.

Data were analyzed using SPSS version 22.0. The normality of data was assessed using Kolmogorov-Smirnov test. The difference in data with skewed distribution was analyzed using Wilcoxon signed rank test while paired samples with normal distribution were analyzed using Paired sample t test. Data are expressed as mean±standard deviation. A p value<0.05 was considered as statistically significant.

RESULTS

The study included 27 eyes of 27 patients with PCME. The normal, contralateral eyes were used as controls. Of the patients included, 12 (45%) were women and 15 (55%) were men. Mean age was 71.33±7.12 among patients included. In the patient group, baseline and final acuity was 0.48±0.23 logMAR and 0.1±0.096 logMAR, respectively (p=0.000). Mean recovery time was 2 months (1-3 months). It was found that mean recovery time showed moderate, negative correlation with baseline and final visual acuity (p=0.001 for each). When the patient group and controls were compared, it was found that there was significant thinning in inner retinal layer thickness (M1), photoreceptor thickness (M2), central foveal thickness in all 9 quadrants based on ETDRS (Table 1). Figure 1 shows M1 and M2

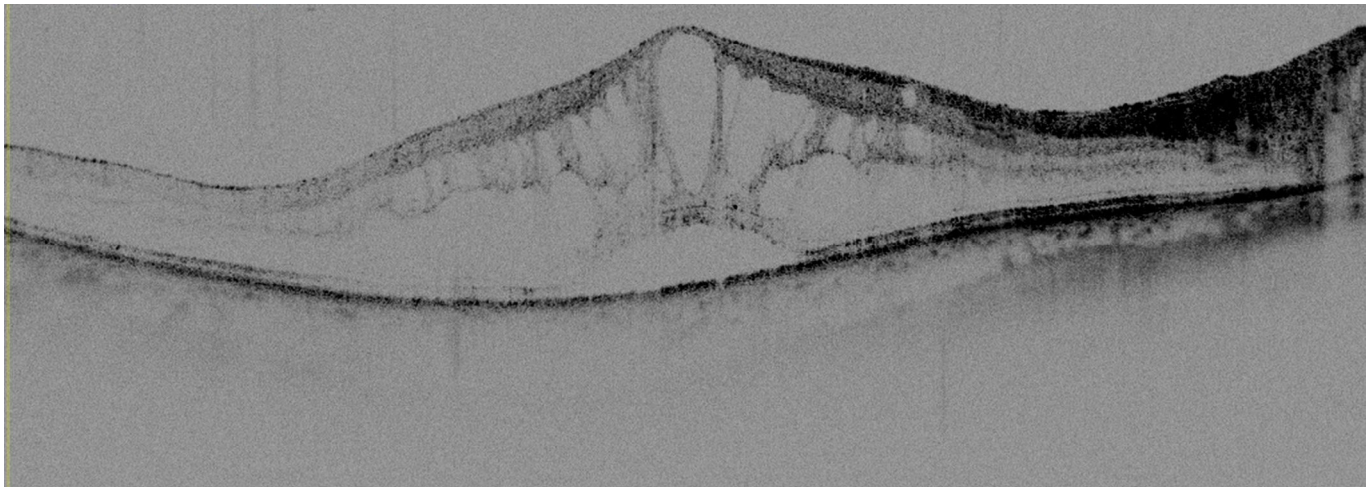

Figure 1: *Postoperative cystoid macular edema.*

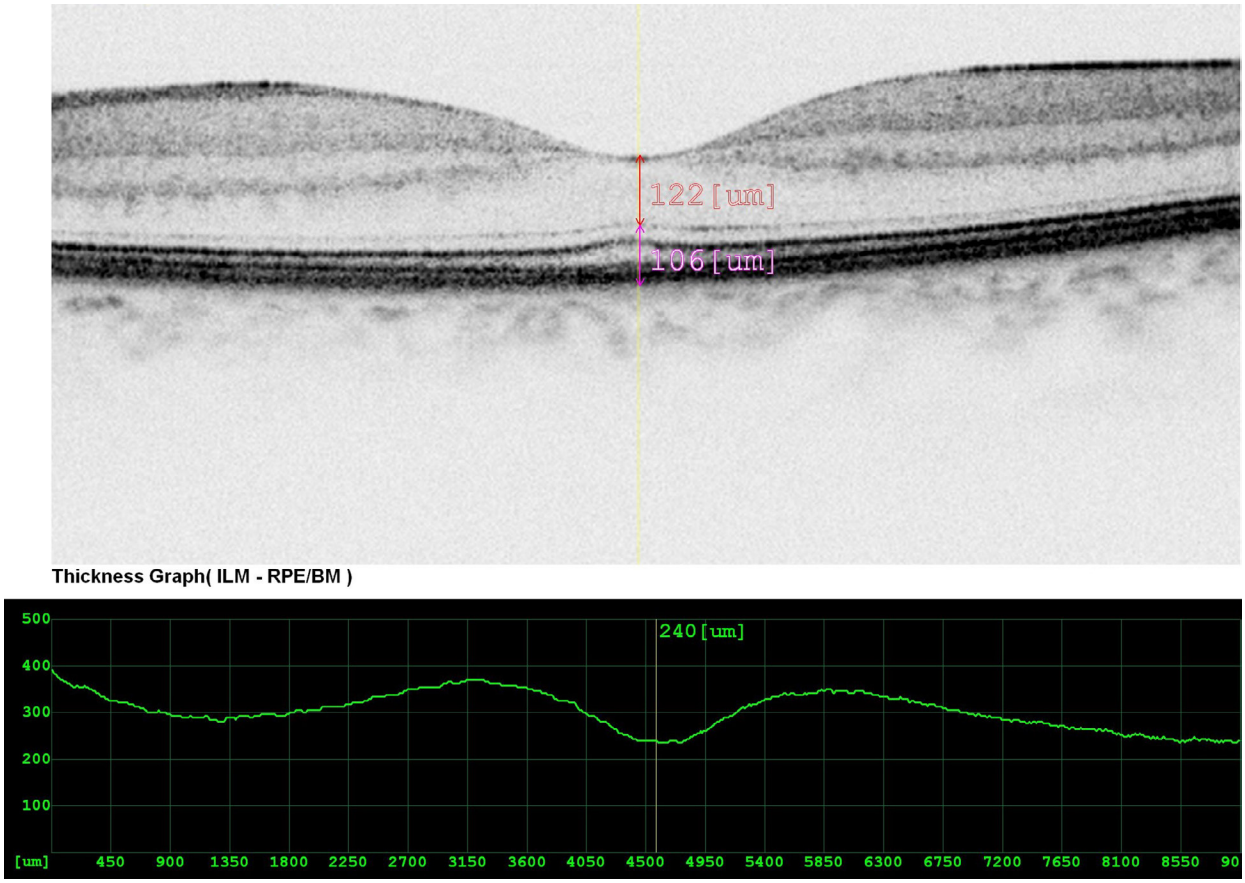

Figure 2: *M1 and M2 measurements in healthy phakic eyes.*

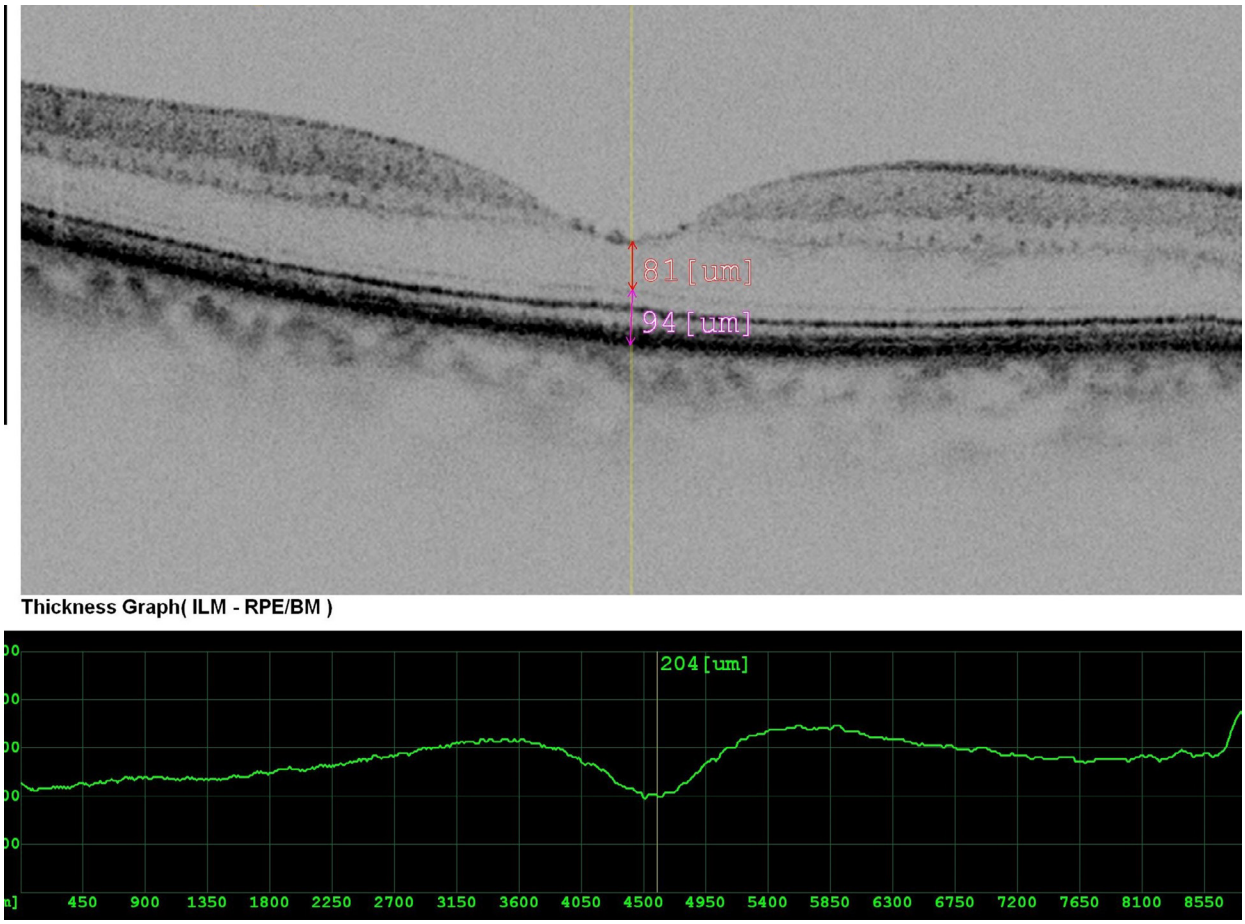

Figure 3: *Atrophic M1 and M2 measurements in non-resistant pseudophakic cystoid macular edema .*

Table 1: *Comparison of macular thickness between PCME and control groups.*

MaCular Segment(µ)	PCME (n=27)	Control (n=27)	*p**
Macular volume	7.52±0.29	8.55±0.22	**0.000
M2	87.37±12.71	102.93±6.27	**0.000
M1	109.22±24.59	131.48±28.77	**0.000
Foveal MT	263.92±20.14	280.81±9.19	**0.000
Mean MT	288.23±9.27	301.61±7.08	**0.000
Inner temporal Mt	299.33±11.40	314.29±10.55	**0.000
Inner nasal MT	300.67±11.91	315.07±15.33	**0.000
Inner superior MT	297.89±20.69	315.22±15.47	**0.000
Inner inferior MT	300.67±14.72	318.33±13.14	**0.000
Outer temporal MT	276.70±13.94	288.70±11.05	**0.000
Outer nasal MT	289.25±15.28	298.78±12.65	**0.000
Outer superior MT	284.48±15.98	292.67±12.62	*0.000
Outer inferior MT	281.19±12.46	290.59±10.35	*0.000

*MT. Macular thickness, µ=Micron *Paired samples t test, **Wilcoxon signed rank test, Presented as mean±standard deviation*

values with atrophy. Similarly, significant thinning was observed in ganglion cell complex (GCC) (Table 2). M1 was 109.22±24.59 µ and 131.48±28.77 µ in PCME eyes and control eyes, respectively (p=0.000). In PCME eyes, a strong positive correlation was detected M1 and visual acuity after treatment (p=0.000). M2 was 87.37±12.70 µ and 102.92±6.27 µ in PCME eyes and control eyes, respectively (p=0.025). Mean macular thickness was 288.23±9.27 µ in PCME eyes whereas 301.61 ±7.08 µ in control eyes. Mean CFT was 263.92±20.14µ in PCME eyes whereas 280.81±9.19 µ in control eyes. Mean macular volume was 7.52±0.28 in PCME eyes whereas 8.55±0.22 in controls, indicating significant difference. Mean GCC thickness was 98.40±4.43 µ in PCME eyes and 103.44±5.43 µ in control eyes (p=0.000). Table 1 and 2 present significant thinning in all other macula and ganglion layers.

DISCUSSION

Pseudophakic cystoid macular edema, in which pro-inflammatory mechanisms are implied, can be defined as

Table-2: *Comparison of ganglion cell complex thickness in PCME and control group.*

Ganglion Cell Complex	PCME (n=27)	Control (n=27)	*p**
Mean GCC	98.40±4.43µ	103.44±5.43µ	**0.000
Inner temporal superior GCC	105.22±8.72µ	112.81±6.28µ	**0.000
Inner temporal inferior GCC	100.59±6.78µ	107.74±8.02µ	**0.001
Inner nasal superior GCC	103.37±8.35µ	110.85±7.81µ	**0.001
Inner nasal inferior GCC	102.44±6.55µ	110.48±8.00µ	**0.000
Outer temporal superior GCC	90.85±7.91µ	94.96±4.91µ	*0.026
Outer temporal inferior GCC	91.00±4.82µ	95.67±3.95µ	*0.000
Outer nasal superior GCC	95.52±9.71µ	101.89±9.42µ	**0.000
Outer nasal inferior GCC	99.00±9.23µ	103.41± 8.34µ	**0.004
Mean GCC	98.41±4.43µ	103.44±5.44µ	**0.000

GCC*: Ganglion cell complex; µ:micron, *Paired samples t test, **Wilcoxon signed rank test, Presented as mean±standard deviation*

clinical process which develops following cataract surgery and causes loss of vision at postoperative period. In many studies including animal studies, pro-inflammatory mediators are implied in PCME pathophysiology. These mediators include prostaglandins, platelet activating factor (PAF) and VEGF.[6, 10] In many studies, it has been proposed that inner and outer blood-retina barriers are disrupted as a result of pro-inflammatory process, resulting in edema by increasing vascular permeability.[6, 9, 10] However, its pathophysiology hasn't been fully elucidated; thus, there is no consensus in the treatment.

Although topical NSAIDs together with follow-up are used to suppress inflammation, some cases may be resistant regarding recovery of macular edema; thus, loss of vision persists. In such cases, intravitreal steroid or anti-VEGF agents are used.[11, 12] In our study, topical treatment was given to the patients who were then followed. Although vision was improved in our patients, thinning was detected in retinal inner and outer layers, macular volume and ganglion cell complex at long-term. This may be due to several reasons.

The disruption of inner-outer retinal barrier is the most commonly emphasized cause for retinal edema. As suggested in a study on pathophysiology of macular edema, trauma, vascular causes and inflammatory factors lead fluid passage from blood-retina barrier to neurosensory retinal layers. The fluid leads cystoid edema around inner nuclear layer as it is confined by internal and external plexiform layers; fluid accumulation can occur at subretinal area due to RPE and choroid damage and Henle layer can be involved. Again, in that study, it was suggested that glial cells can factors that may increase or decrease tight-junction in endothelium. Authors suggested that the major factor leading increased permeability is VEGF.[14] The VEGF is an important factor which acts on both inner and external retinal barrier. It was shown that, in external retinal barrier, VEGF is continuously released from RPE cells to protect choroidal permeability.[15] On the other hand, it was shown that VEGF is released in pathological conditions such as hypoxia at inner blood-retina barrier.[16]

Several animal studies have been conducted to elucidate PCME pathophysiology. As known, the increased inflammation leads disruption in blood-retina barrier. Many studies showed that inner blood-retina barrier has been affected more significantly. In a study, it was shown that disruption of internal blood-retinal barrier played greater role.[17] In an animal study at molecular level, it as shown that inflammation and complement activation were increased at neurosensory retina at posterior segment after lens removal in rats. In the same study, it was demonstrated that interleukin-1 beta (IL-1ß) is an important mediator, activating complement cascade. It was proposed that increased IL-1ß can potentially enhance vascularization by increasing VEGF expression.[9] In the literature, there are studies supporting that IL-1ß disrupts blood-retina barrier and induces VEGF release.[18-20]

Type and localization of edema are important in macular diseases. Irvine-Gass syndrome mainly causes cystoid edema. Although edema is more commonly seen at inner retinal layer, it may involve all layers including subretinal fluid accumulation. In the literature, there are some studies investigated macular disease in the context of edema pathophysiology. In a study evaluating edema types, it was shown that cystoid fluids were mainly localized at inner and outer nuclear layers. It was suggested that cystoid fluid accumulation at these levels may be suggestive of an exudative mechanism related to leakage from deep capillary plexus.[21] In another study, it was shown that, in PCME, cystoid edema was started from inner nuclear layer and extended to outer nuclear layer and even up to subretinal area. In the same study, it was shown that it was most commonly seen at inner nuclear layer. It has been proposed that cystoid change in inner nuclear layer may be earliest marker of inflammation. It was suggested that the condition may remain subclinical or result in diffuse edema. The authors proposed that pro-inflammatory cytokines can increase hyper-permeability of mid-capillary plexus. The increased inflammation in the branches of this plexus surrounding inner nuclear layer may explain why the process starts at inner nuclear plexus.[22] In our patient group, cystoid edema was present solely at inner nuclear layer on OCT images from patients with impaired vision at early phase. We think that inflammatory cystoid edema, which can remain as subclinical, may be present at inner nuclear layer although it is not clinically apparent.

In a study using OCT angiography (OCTA), a significant reduction was observed in superficial and deep capillary plexuses in patients with Irvine-Gass syndrome when compared to controls.[23] In our study, inner retinal layer, measured as M1, was found to be significantly thinner in PCME eyes when compared to control eyes in our study. We think that this finding is supportive for more common involvement of inner retinal layers in PCME and that inner retinal barrier is affected mainly. We think that atrophy at inner retinal layers may be increased due to capillary plexus damage by prolonged cystoid edema. In our study, we think that the decreased macular thickness, volume and GCC atrophy may be due to resistant cystoid edema that persisted, although it was subclinical. In an Australian study including 100 eyes, OCT measurements were performed on week 1, 4 and month 6 in eyes with PCME and a significant increase was detected in central foveal

thickness on week 4; which returned preoperative values on month 6.[24] In the same study, a significant reduction was detected on week 4 when compared to month 6 despite lack of atrophy. Numerically, it was approximately 400 µ on week 4 and decreased to 250 µ on month 6. Authors did not consider this reduction as atrophy; however, it can be thought that atrophy may develop at long-term given these results.

In the literature, there is a study the significance of neurosensory retinal layer enlargement can be due to compartment syndrome caused by cystoid dilatations and decreased perfusion at inner layers resulting from such compression.[25] In our study, the significant thinning in macular layers and GCC may largely be due to effect of compartment effect of edema at inner neuroretinal layer .

In a study on diabetic macular edema, cystoid spaces was completely lacking of capillary flow on OCTA and capillary flow was observed at areas of cystoid edema following anti-VEGF therapy. Authors interpreted this finding as recovery of perfusion after anti-VEGF therapy.[26] We think that delayed anti-VEGF or intravitreal dexamethasone therapy during widely accepted topical therapy may disrupt perfusion of inner retinal layers due to increased inflammation of mid-capillary plexus, which, in turn, may present as subclinical atrophy such as M1 thinning. The significant thinning detected in GCC layers can result from subclinical atrophy at foveal area (Table 2). We believe that the inflammation can increase damage in retinal layers in parallel to its duration.

This study has some limitations including limited sample size; however, PCME incidence has been decreased after advances in phacoemulsification technology.

In conclusion, the PCME, which is mostly treated with topical therapy and follow-up, can be detected by widespread use of OCT even it is subclinical and can lead atrophy in retinal layers by prolonging cystoid edema although functional vision can be recovered. It should be kept in mind that future retinal atrophy can be prevented by decreasing recovery time with earlier single dose intravitreal therapies rather than long-term topical therapy.

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