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Clinical and spectral-domain optical coherence tomography findings and changes in new-onset macular edema after silicone oil tamponade

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Abstract

Backgroud Few investigations have been conducted on the detailed clinical features of CME associated with SiO, from emergence to restoration, especially using OCT images. This study aimed to analyze the clinical and spectral-domain optical coherence tomography (SD-OCT) characteristics and changes in cystoid macular edema (CME) associated with silicone oil (SiO).

Methods Retrospective case series. Six cases of newly on-set CME after SiO tamponade were examined. SD-OCT was performed before pars plana vitrectomy, after SiO tamponade, and after SiO removal. Clinical and SD-OCT data was collected.

Results CME was first noted at 28.83 ± 9.22 days after SiO tamponade. The average foveal thickness was 411 ± 41 μm before oil removal and decreased to 267 ± 69 μm three days after oil removal ($P = 0.028$). The average visual acuity before and after oil removal were 0.82 ± 0.40 logarithm of the minimum angle of resolution (logMAR) and 0.75 ± 0.45 logMAR, respectively, and the difference was not statistically significant ($P = 0.285$). SD-OCT revealed that three patients had edema first in the inner nuclear layer (INL), and three had cysts in both INL and outer nuclear layers (ONL) at discovery. Of the six patients, three exhibited cystic changes in the fovea firstly. CME showed rapid recovery following SiO removal, with cysts completely disappearing in four patients (66.7%) within 3 days. However, in two patients (33.3%), the cysts persisted in INL after three days, whereas the cysts in ONL had resolved completely. The ellipsoid zone integrity of the macular region was smoother in patient with better vision.

Conclusion New-onset CME after SiO tamponade may initially affects INL and then ONL. CME shows significant improvement after oil removal, probably initially resolving in ONL, and then followed by INL. SD-OCT enabless monitoring of macular microstructure changes in SiO-treated eyes, and macular cysts' occurrence can indicate the oil removal need.

Keywords Cystoid macular edema, Spectral domain optical coherence tomography, Silicone oil eyes, Silicone oil removal

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Background

Cystoid macular edema (CME) is a commonly seen retinopathy characterized by macular thickening with intraretinal fluid accumulation, which can cause decreased vision [1]. It is a complication of a wide spectrum of retinal diseases, including diabetic retinopathy (DR), retinal vein occlusion (RVO), uveitis, exudative age-related macular degeneration (AMD), and retinitis pigmentosa (RP) [2]. CME associated with silicone oil (SiO) is also reported in recent years [3–5].

SiO is widely used in vitrectomy surgery. Even if the retina is successfully attached after SiO tamponade, CME can lead to a poor prognosis [6]. Spectral-domain optical coherence tomography (SD-OCT) can provide in vivo high-resolution cross-sectional images of the retina even through intraocular SiO. Therefore, the microstructural changes of the macula under SiO tamponade can be demonstrated and monitored clinically using SD-OCT. Previous study had also demonstrated SD-OCT has a higher ability than FA in characterizing the existence of CME [7]. However, to the best of our knowledge, few investigations have been conducted on the detailed clinical features of CME associated with SiO, from emergence to restoration, especially using OCT images. This study aimed to observe the formation time and characteristics of new-onset CME after vitrectomy with SiO tamponade, the changes in CME during SiO tamponade, and after SiO removal using SD-OCT.

Methods

This study adhered to the tenets of the Declaration of Helsinki. Surgeries were performed after obtaining informed consent from all patients. Six consecutive patients who were diagnosed with CME during SiO tamponade after vitrectomy for rhegmatogenous retinal detachment or diabetic retinopathy between 2014 and 2022 were retrospectively enrolled. A standard three-port 23-gauge pars plana vitrectomy (PPV) approach by Alcon Constellation (Alcon Laboratories, USA) was used in all the cases. The 4 surgeons were all experienced retina specialist with no obvious technique difference. The silicone oil was the same (Oxane 5700, Bausch & Lomb). All patients met the inclusion criteria that the eyes had newly developed CME after SiO filling and that they underwent SiO removal alone in the later stage. The exclusion criteria were CME before surgery (Preoperative CME was carefully excluded using combined clinical and OCT assessments. However, we acknowledge that OCT imaging in macula-off retinal detachment poses technical challenges, which may limit the detection of subtle preoperative abnormalities.), CME accompanied by a macular epiretinal membrane, SiO removal surgery combined with internal limiting membrane peeling or intraocular drug injection, and incomplete clinical data.

All eyes underwent complete ocular examination, including slit-lamp examination and binocular indirect ophthalmoscopy. The clinical data collected included age, sex, eye laterality, medical history, ophthalmic history, intraocular pressure, lens status, macular status (on or off) before surgery, axial length, recorded time of CME, and best-corrected visual acuity (BCVA) before and after silicone oil removal. SD-OCT was used to identify CME, observe changes in macular microstructure during different stages, and measure the average thickness of the macular fovea before and after SiO removal. SD-OCT was given routinely before SiO tamponade, within 1 week after SiO tamponade, 3–5 weeks after SiO tamponade, before SiO removal, within 1 week post-removal, 1 month or more post-removal.

Axial length was measured using an IOL-Master 500 (Carl Zeiss Meditec, Jena, Germany). OCT scanning was performed using Spectralis (Spectralis HRA-OCT, Heidelberg Engineering, Heidelberg, Germany) or Cirrus HD-OCT (Carl Zeiss Meditec, Inc. Dublin, California, USA). Images were obtained from a 30×30 degree (9×9 mm) scan area consisting of 12 sections using radial scan patterns obtained using Spectralis HRA-OCT. A macular Cube 512×128 mode length of 6 mm or HD 5-line raster scan mode with a length of 6–9 mm was used for Cirrus HD-OCT. Four eyes were examed by Cirrus HD-OCT and two eyes by Spectralis HRA-OCT. For each patient, the same device was used at different follow-up time. The OCT images were interpreted independently by two authors (J.X.B and X.Z), and a consensus was reached. SD-OCT examinations mainly focused on the ellipsoid zone and/or external limiting membrane (EZ/ELM) damage, the presence and characteristics of CME, and central macular thickness (CMT). EZ line scoring method was applied, following criteria established in prior literature [8]. grade 0: lack of the EZ line, grade 1: the reflectivity of the EZ line similar to the reflectivity of ELM, grade 2: the reflectivity of the EZ line higher than the reflectivity of ELM but lower than that of RPE, grade 3: the reflectivity of the EZ line similar to that of RPE. CME was defined as the presence of intraretinal cystoid changes and intra-retinal hyporeflective areas separated by hyperreflective septa and sometimes a loss of foveal depression. The characteristics of macular edema were mainly focused on the retinal layer where the cystic change first appeared, the involved layers, the area where the cystoid change first appeared, and subsequently, the involved areas, the layer where CME first disappeared, and whether there was subretinal fluid (a hyporeflective space between the neurosensory retina and the RPE). CMT was measured automatically by the software in the device and manually adjusted if the automatic outline was incorrect.

Snellen visual acuity was converted to the logarithm of the minimum angle of resolution (logMAR) equivalent for analysis. Statistical analyses were performed using SPSS statistical software (version 26, IBM SPSS Statistics). Statistical significance was set at $P<0.05$. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as individual counts and proportions. The Wilcoxon rank sum test was used to compare CMT and BCVA before and after SiO removal, and Spearman's rank correlation coefficient test was used to compare the trend between EZ score and CMT or BCVA before SiO removal.

Results

During this period, 111 silicone oil removal surgeries were performed due to rhegmatogenous retinal detachment or diabetic retinopathy. 87 eyes had no edema after SiO tamponade. 5 eyes were excluded because of macular edema before surgery, 10 eyes because of CME accompanied by epiretinal membrane, 2 eyes because of intravitreous triamcinolone acetonide injection after silicone oil removal, and 1 eye was excluded because of incomplete clinical data. This study included six patients (male: 5; female; 1, right eye 2; left eye 4). Of the six included patients, the original PPV was performed for rhegmatogenous retinal detachment in four eyes and diabetic retinopathy in two eyes. The lens status included four pseudophakia and two phakia cases. Retinal detachment involved the macula in four cases (66.7%), and the macula was attached preoperatively in two cases (33.3%). Of the two diabetic retinopathy patients, one eye had the macula-off, and one had the macula-on. Three eyes exhibited macular involvement at presentation, and the other eye did not affect the macula in the four rhegmatogenous retinal detachment patients. The age range of the patients was 35–69 years (55.5 ± 12.63 years). The axial length ranged from 23.29 to 28.75 mm (24.96 ± 2.51 mm). CME did not appear at the first follow-up within 7 days. CME was first noted at the second follow-up time 19–42 days (28.83 ± 9.22 days) after SiO tamponade. SiO tamponade time ranged from 48 to 137 days, with an average of 84.5 ± 37.69 days.

The average foveal thickness of the macula was 411 ± 41 μm before oil removal and decreased to 267 ± 69 μm three days after oil removal ($P=0.028$). The average visual acuity pre-removal was 20/125 ± 20/50 (0.82 ± 0.40 logMAR), and the average visual acuity 3–4 days post-removal was 20/100 ± 20/50 (0.75 ± 0.45 logMAR), and the difference was not statistically significant ($P=0.285$).

The clinical and OCT data of the six patients with CME are summarized in Table 1. The OCT features and changes in the CME before and after silicone oil removal are shown in Figs. 1, 2, 3 and 4. SD-OCT revealed that three (50%) of the six patients had edema first in the inner nuclear layer (INL), and three patients had cysts in both the inner and outer nuclear layers (ONL) at the time of discovery. One of the three patients with edema first in the INL underwent SiO removal immediately (Fig. 2), and the other two patients had edema that spread to the ONL with an extension of the filling time (Fig. 3). Of the six patients, three (50%) had cystic changes in the fovea first, one in the nasal parafovea region; the macular edema in the above four patients showed symmetrical changes before SiO removal (Figs. 2, 3 and 4), but the cysts demonstrated mild asymmetry in distribution and size in the other two patients, of which one patient was found to have edema in the temporal parafovea region and one in the fovea and temporal parafovea region (Fig. 1). From Figs. 1, 2, 3 and 4, we can see that after long-term SiO filling, the macular edema became diffuse, involving the inner and outer nuclear layers, the absence of subretinal fluid, and an almost symmetric appearance. CME showed rapid recovery following SiO removal, with cysts completely disappearing in four patients (66.7%) within 3 days. However, in two patients (case 3/4), the cysts persisted in INL after three days, whereas the cysts in ONL had resolved completely. When there was still a cystic change on OCT after one month, we called it lack of completely recovery. Patients 3 and 4 were followed up 2 months and 1 month after oil removal, respectively. OCT images were the same as in the early stage post-removal, and still showed cystic degeneration in INL. Both patients were subsequently lost follow-up.

Morphological analysis via SD-OCT revealed that pre-SiO removal BCVA was correlated with the integrity of the EZ, with a higher EZ band score associated with better VA (r=-0.939, $P=0.005$). However, the EZ band score showed no correlation with pre-removal macular thickness (r=-0.494, $P=0.320$).

Discussion

Our study found that CME associated with SiO first appeared in the INL in 3 cases, then involved the ONL over time, and 3 had cysts in both INL and ONL at discovery. Though concurrent cyst formation cannot be ruled out, this observation may suggest a temporal progression hypothesis that INL cysts developed prior to ONL involvement if earlier OCT scans were available. The cysts appeared first mostly in the fovea; however, it could also appear in the nasal or temporal fovea first and then spread to the fovea. When the retina was well reattached without a macular epiretinal membrane, CME completely disappeared 3 days after simple SiO removal in 4 patients. In the two patients whose macular edema did not completely disappear promptly after SiO removal, cysts in the ONL disappeared first, and cysts in the INL remained at the limited follow-up time.

Table 1 Clinical and SD-OCT findings and changes of CME patients

No.	1	2	3	4	5	6
Age(yrs)/Eye /Diagnosis	69/OS/PDR	47/OD/RRD	58/OS/RRD	66/OS/RRD	58/OS/RRD	35/OD/PDR
Macular involvement	No	No	Yes	Yes	Yes	Yes
Axial length(mm)	23.29	28.75	23.45	27.55	23.50	23.19
Surgery	PPV + SiO	PPV + *P* + I + SiO	PPV + *P* + I + SiO	PPV + *P* + I + SiO	PPV + SiO	PPV + SiO
Discovery time of CME (days)	24	42	19	20	34	34
Duration of SiO filling(days)	90	48	120	137	63	49
Lens status before SiO removal	pseudophakia	pseudophakia	pseudophakia	pseudophakia	phakia	phakia
CMT before SiO removal(μm)	412	358	444	434	365	455
CMT after SiO removal(μm)	168	257	207	340	295	334
BCVA before PPV surgery (LogMAR)	0.7	0.4	2.0	0.2	2.0	1.7
BCVA 3 days after PPV surgery (LogMAR)	0.4	0.4	1.3	0.2	0.6	1.3
BCVA before SiO removal (LogMAR)	1.3	0.5	1.3	0.4	0.6	0.8
BCVA after SiO removal (LogMAR)	1.3	0.2	1.3	0.4	0.6	0.6
Timing of OCT after SiO tamponade (days)	3/24/60/90	7/42/48	7/19/32/60/120	2/20/90/135	6/34/60	6/34/40
Timing of OCT post SiO removal	3d/1m/6m/8m	3d/1m/6m	4d/1m	4d/2m	3d/1m	3d/3m/4m/7m
EZ score before SiO removal (0 ~ 3)	0	1	0	2	1	0
OCT characteristics of CME with SiO						
Layers cysts first appear	Not captured	INL	INL	Not captured	Not captured	INL
Layers cysts involved	INL & ONL	INL	INL & ONL	INL & ONL	INL & ONL	INL & ONL
Location cysts first appear	F & temporal F	F	Nasal F	F	F	Temporal F
Location cysts involved	F & parafovea	F	F & parafovea	F	F & parafovea	F & temporal F
OCT changes of CME after SiO removal						
Completely recovery	Yes	Yes	No	No	Yes	Yes
Days cysts completely disappear(days)	3	3	-	-	3	3
Layers cysts first disappear	Not captured	Not captured	ONL	ONL	Not captured	Not captured

OS: left eye; OD: right eye; PDR: proliferative diabetic retinopathy; RRD: rhegmatogenous retinal detachment; PPV: pars plana vitrectomy; SiO: silicone oil; P: phacoemulsification; I: intraocular lens implantation; CME: cystoid macular edema; BCVA: best corrected visual acuity; INL: inner nuclear layer; ONL: outer nuclear layer; F: fovea; d: day; m: month

In this study, three of the six patients (cases 1, 2, and 4) showed a gradual decrease in visual acuity after CME. Three or four days after SiO removal, the visual acuity in cases 1 (20/400) and 4 (20/50) did not improve; however, the CME disappeared or recovered significantly, whereas the visual acuity (20/67) in case 2 improved to 20/33 which is the BCVA before the CME formation after SiO filling. The visual acuity of the other three patients with macular-off improved after retinal reattachment. The SiO was removed once CME was detected in cases 5 and 6, and no further VA decline was observed due to CME. The visual acuity of case 3 before vitrectomy was only hand motion; the BCVA improved to 20/400 19 days after retinal reattachment, and vision did not further improve after the occurrence of CME and did not decline. Several hypotheses have been proposed to explain why CME causes a decrease in vision. This may be due to the failure of Müller cells to siphon potassium out of the retina, high transmission of toxic blue light, or destruction of the inner retinal layers. Simultaneously, CME is often accompanied by damage to the EZ/ELM, which is also one of the reasons for vision decline [1, 9–11]. In this study, patients with better vision before SiO removal showed better continuity of the EZ. Over time after SiO removal, the EZ/ELM gradually recovered to its preoperative condition.

Macular edema can occur due to increased fluid entry through either the inner or outer blood-retinal barriers. Breakdown of the inner barrier is mainly due to the alteration of intercellular junction proteins, increased transendothelial transport, and loss of cells constituting the barrier. The dysregulation of the outer barrier is primarily due to the damage of RPE cells and the destruction of the outer limiting membrane [1]. In general, the leakage of blood vessels in the INL leads to cysts formation in the INL, and the transcellular water movements in inner retina are mainly managed by Müller cells, whereas RPE cells are mainly responsible for the outflow of water in the outer retina, edema occurs in Henle's fiber layer and ONL when the function of RPE cells is impaired [12]. Studies have shown that the aquaporin (AQP) family and the active and passive mechanisms of K + current regulation maintain the balance of retinal fluid entry and outflow; however, the full spectrum of molecular signals that control hydro-ionic retinal homeostasis remains unclear [1]. AQP-4 and Kir4.1 potassium ion channel proteins are highly expressed in Müller cells, and AQP-1 channel protein is mainly expressed in RPE cells [1].

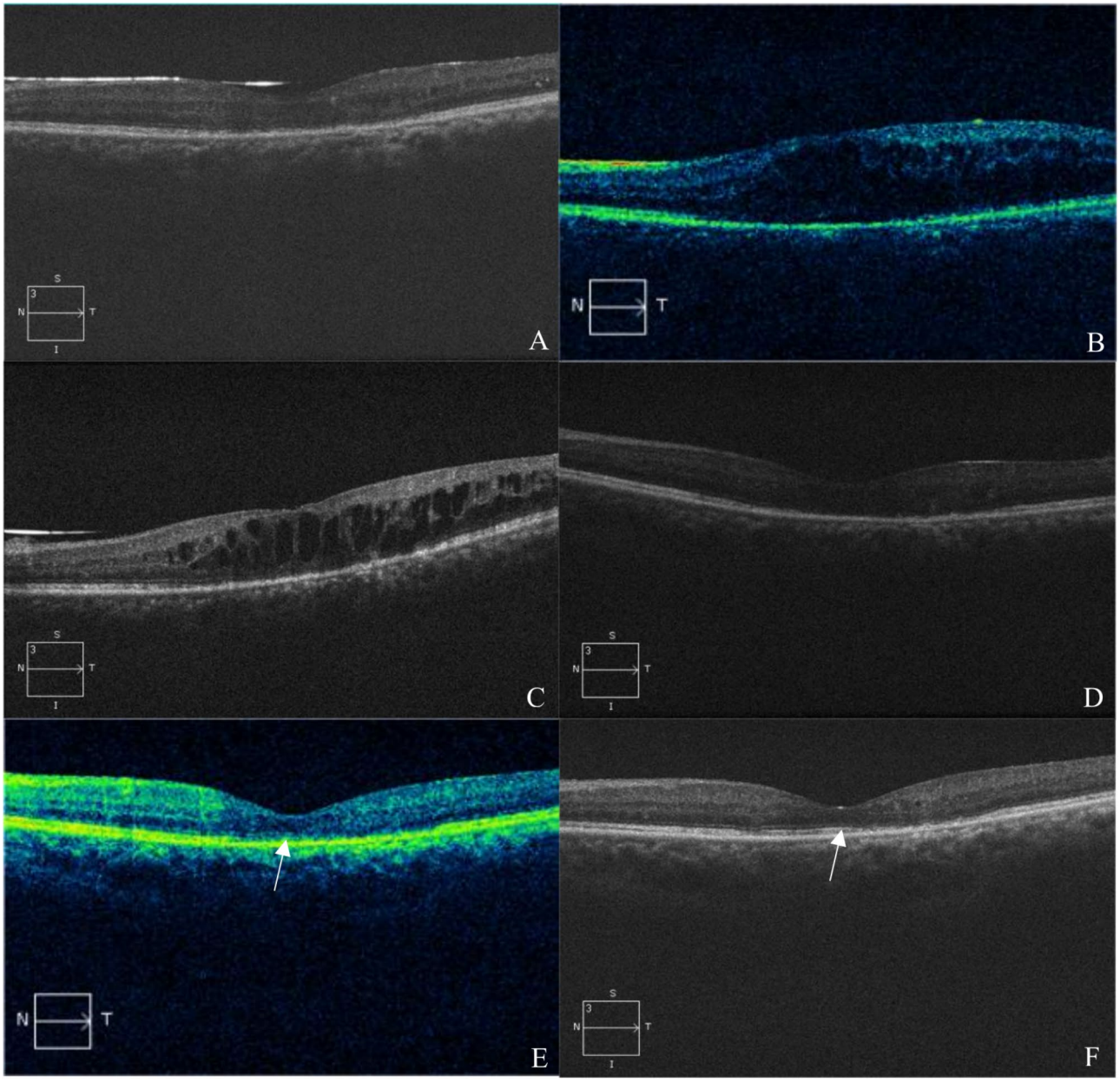

Fig. 1 OCT images of different periods before and after SiO removal in case 1. **A.** The OCT 3 days after SiO tamponade did not show CME. **B.** Cysts appeared in the INL, Henle's fiber layer and ONL on the 24th day. **C.** The CME still existed in the INL, Henle's fiber layer and ONL after 3 months of SiO filling. **D.** CME completely disappeared 3 days after SiO removal, but the EZ/ELM were disrupted. **E.** EZ/ELM were gradually recovering 1.5 months after SiO removal (white arrow). **F.** The continuity of EZ/ELM improved further 6.5 months after SiO removal (white arrow)

Immunolocalization confirmed the decreased expression of Kir4.1 and AQP4 in the diabetic Goto-Kakizaki (GK) rat with a more pronounced reduced distribution in the INL and around the vessels [1]. This study found that SiO-related CME may initially appear in the INL and then progressed to the ONL. We speculated that hypoxia or inflammatory factors in the SiO first irritated the Müller cells and induced the abnormal distribution of potassium ions and aquaporin AQP-4, followed by edema in the INL. When the inducing factors were not removed, it led to abnormal expression of AQP-1 aquaporin in RPE cells, resulting in edema of the ONL. After the SiO was removed, inflammatory factors were redistributed in the vitreous cavity, or the oxygen supply of the retina was improved, and the function of RPE cells was quickly restored, which manifested as cysts in the ONL fading first, and the cysts in the INL gradually disappeared after the function of Müller cells was restored. It is important to note that, due to the lack of intraocular cytokine

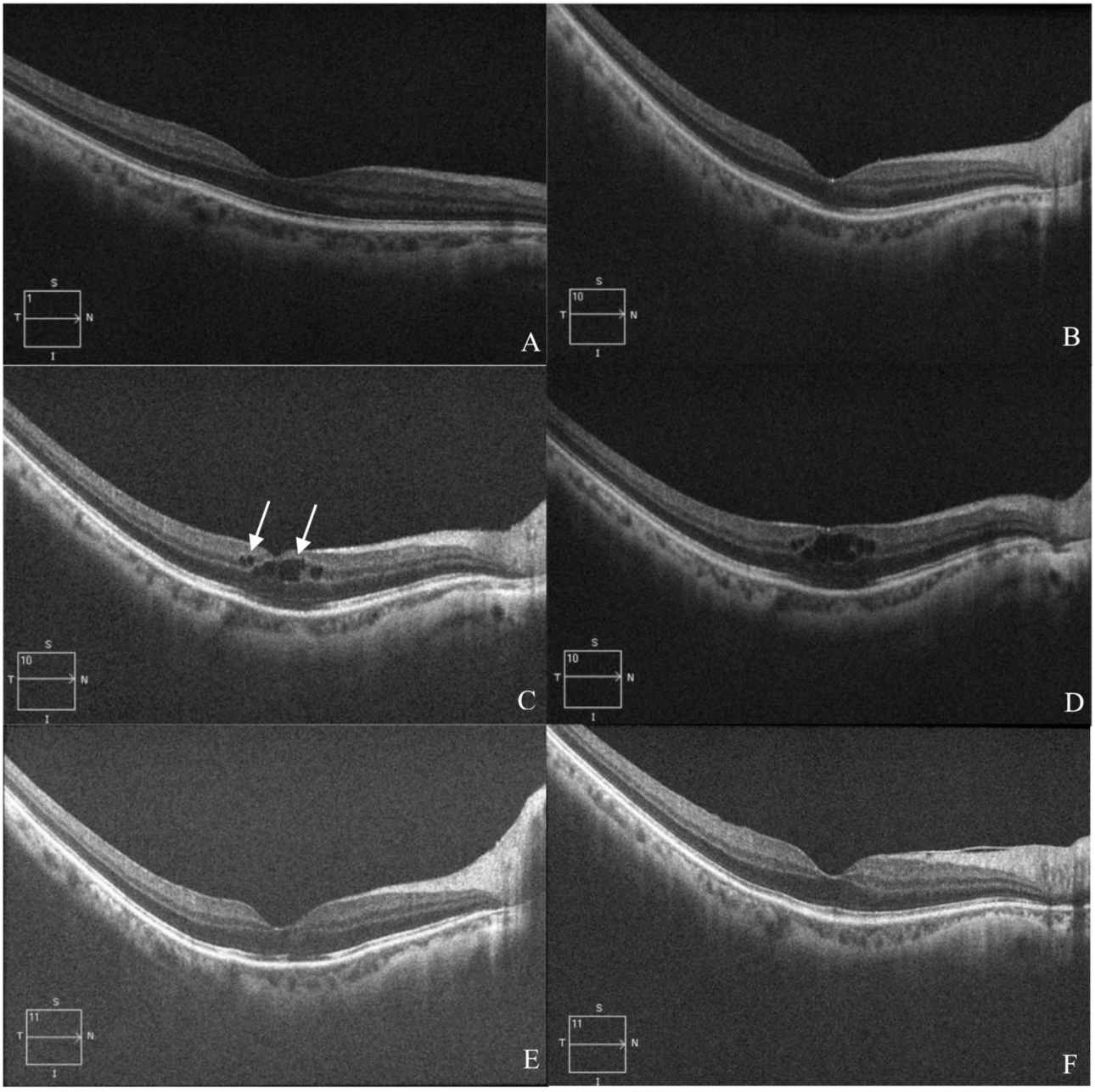

Fig. 2 OCT images of different periods before and after SiO removal in case 2. **(A)** The macular was on without edema before PPV surgery. **(B)** The OCT 7 days after SiO tamponade showed smooth reflection of macular microstructure. **(C)** The cysts (white arrow) first formed in INL 42 days after SiO tamponade, and EZ/ELM were continuous. **(D)** The cysts fused 48 days after SiO tamponade, and no obvious defect was found in EZ/ELM. **(E)** CME disappeared completely 3 days after SiO removal. **(F)** EZ/ELM reflection was smooth 6 months after SiO removal

detection in our study, we cannot exclude the potential interplay within the hypoxia-inflammation-VEGF axis.

From the above analysis, we believe that the appearance of CME in patients with SiO tamponade is a sign of vision loss and that CME may indicate the impaired function of Müller cells and RPE cells. SD-OCT can detect changes in the macular microstructure over time before obvious changes in visual acuity. We suggest that SiO removal should be performed as soon as possible if the retina is well reattached when cystic changes occur in the macula.

Previous studies on the effects of SiO on the retina have mainly focused on whether it would cause changes in the nerve fiber layer or the continuity of EZ/ELM [3, 6, 11, 13–17]. Few studies exist on new-onset CME during SiO filling. Shalchi et al. [3] found that when patients with long-term SiO tamponade showed unexplained vision loss accompanied by macular edema, OCT revealed

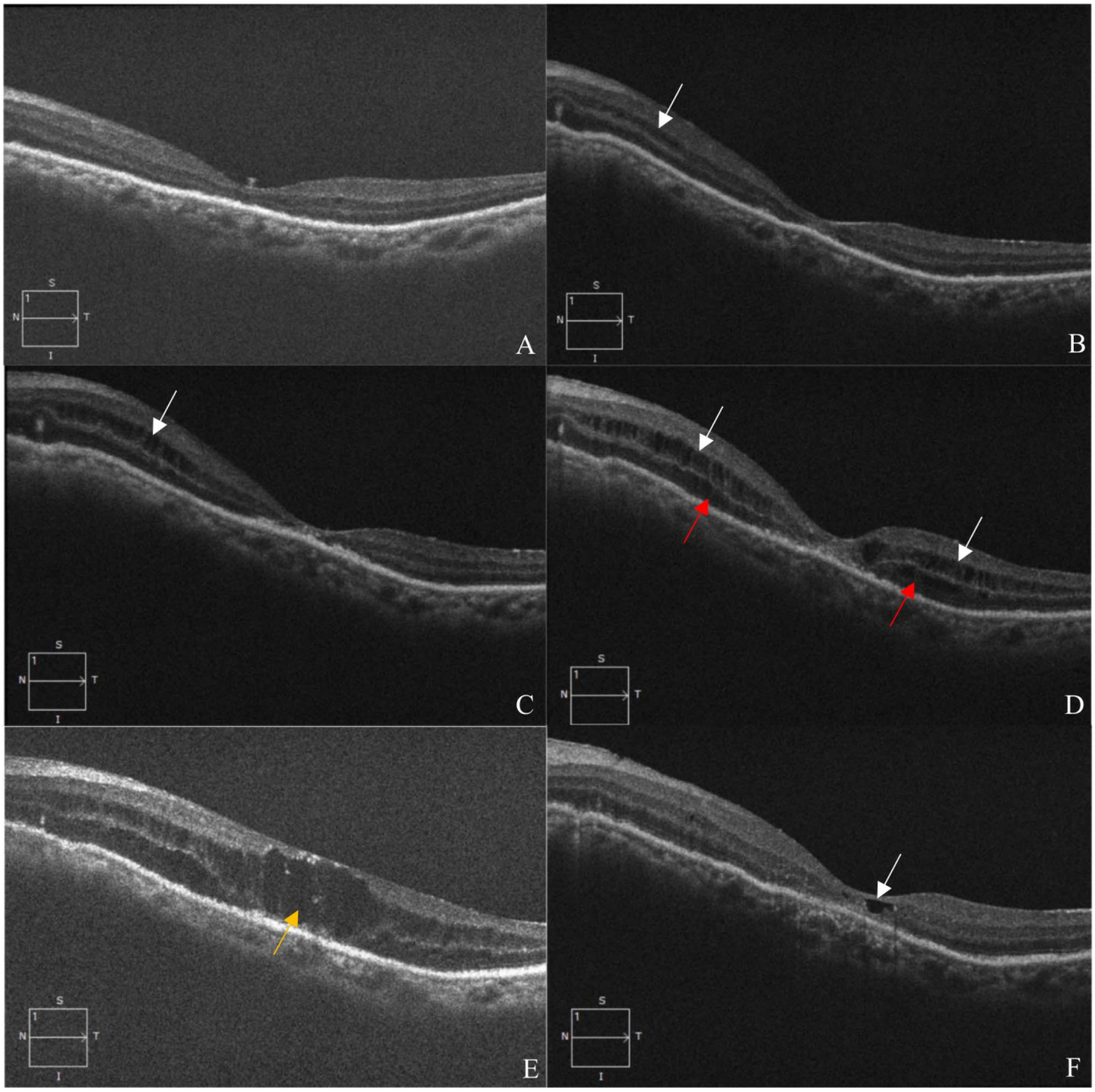

Fig. 3 OCT images of different periods before and after SiO removal in case 3. **(A)** The OCT 7 days after SiO tamponade did not show CME. **(B)** Cysts appeared in the INL nasal to the fovea on the 19th day, as shown by white arrow. **(C)** INL cysts nasal to the fovea became enlarged and obvious 22 days after SiO tamponade. **(D)** The cysts involved INL around the fovea (white arrow) and extended to the ONL (red arrow). **(E)** CME spread to Henle's fiber layer in the fovea (yellow arrow). **(F)** CME disappeared in ONL 4 days after SiO removal, but not totally in INL (white arrow)

microcystic changes in the INL, which appeared preferentially in the nasal macula and produced an incomplete annulus around the fovea that only completed a full circle when severe. Lo et al. [5] found that the CME disappeared after SiO removal, which is consistent with the results of our study. However, the included patients with CME were those with tractional retinal detachment caused by diabetic retinopathy, who showed CME before SiO tamponade and were further aggravated during SiO tamponade, which was different from our included population. Bae et al. [18] found that in patients with CME combined with the macular epiretinal membrane during SiO tamponade, CME could vanish when the epiretinal and internal limiting membranes were peeled off simultaneously. They also found that CME recovered after SiO removal alone in two patients without an epiretinal membrane. Although they described the phenomenon that both CME and subretinal fluid could disappear after

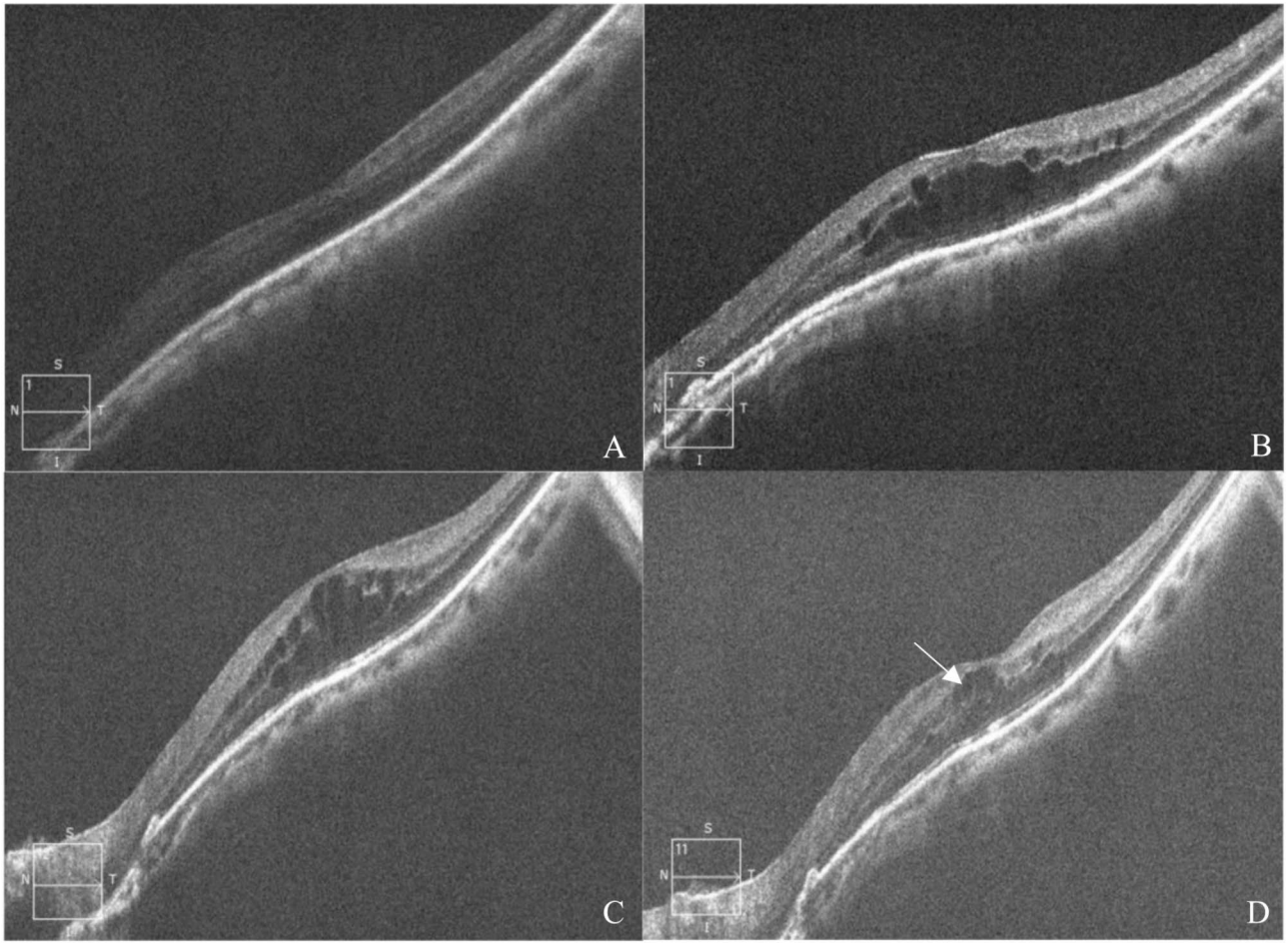

Fig. 4 OCT images of different periods before and after SiO removal in case 4. **(A)** The OCT 2 days after SiO tamponade did not show CME. **(B)** The cysts appeared in the INL and Henle's fiber layer 20 days after SiO tamponade. **(C)** There was no significant change in CME 4.5 months after SiO tamponade. **(D)** The CME recovered significantly 3 days after SiO removal, cysts in the Henle's fiber layer almost completely subsided, but a few remained in the INL (white arrow)

SiO removal, they did not describe or analyze the specific morphology of CME formation, development, and regression. This study presents longitudinal OCT images capturing structural changes at multiple time points preceding and following CME development. New-onset CME after SiO filling is a relatively uncommon postoperative complication. In Bae's study on macular microstructure before and after silicone oil removal, 3/46 eyes had CME without epiretinal membrane [18], while Pole et al. [4] found that the incidence of CME without epiretinal membrane after RRD repair surgery was 7/99. In our study, the occurrence rate of CME without epiretinal membrane was 9/111.

The advantage of this study is that all patients underwent OCT examination before and after SiO tamponade as well as after SiO removal. The diagnosis of CME was definite, and changes in CME in the eyes with SiO were dynamically observed. Our study had some limitations: (1) This was a retrospective study with a small number of cases. (2) In our clinical practice, patients after PPV with SiO tamponade were instructed to undergo an OCT examination 3–7 days, one month, two months, and three months postoperatively. OCT measurement cannot reach daily monitoring, and some patients do not strictly follow up at the required time; therefore, the discovery time of macular microstructure change may be inconsistent with the real formation time. (3) Long-term follow-up visual acuity and OCT data after SiO removal were lacking.

Conclusions

We found that new-onset CME after SiO tamponade may initially affects INL and then ONL. CME shows significant improvement after oil removal, probably initially resolving in ONL, and then followed by INL. SD-OCT enables monitoring of macular microstructure changes in SiO-treated eyes, and macular cysts' occurrence can indicate the need for oil removal.

Abbreviations

CME	Cystoid macular edema
DR	Diabetic retinopathy
RVO	Retinal vein occlusion
AMD	Age-related macular degeneration
RP	Retinitis pigmentosa
SiO	Silicone oil
SD-OCT	Spectral-domain optical coherence tomography
PPV	Pars plana vitrectomy
BCVA	Best-corrected visual acuity
EZ/ELM	Ellipsoid zone and/or external limiting membrane
CMT	Central macular thickness
RPE	Retinal pigment epithelium
logMAR	Logarithm of the minimum angle of resolution
INL	Inner nuclear layer
ONL	Outer nuclear layers

Author contributions

JXB and XZ performed the initial clinical database search, identified confirmed cases of newly onset CME with SiO, collected all images and generated descriptive statistics as presented. JXB produced the first draft of the manuscript and figures. XYP, XQZ and JXB contributed to the study concept and design, reviewed statistical analysis and edited the manuscript, contributing to the final version sent for approval. All authors read and approved the final manuscript.

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Data availability

Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate

We adhered to the tenets of the Declaration of Helsinki. Ethics approval was obtained from the the ethics committee of Beijing Tongren hospital. All participants involved were informed of the purpose of this study and an informed consent was obtained from them.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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