Title page

Title: Lamellar Macular Hole Formation in Chronic Cystoid Macular Edema Associated with Retinal Vein Occlusion

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Running title: Lamellar Macular Hole Formation in RVO

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Abstract

Purpose: To report the formation of a lamellar macular hole (LMH) in four eyes with chronic cystoid macular edema (CME) associated with retinal vein occlusion (RVO).

Methods: We reviewed retrospectively the medical records of four patients with chronic CME associated with RVO, in whom LMH formation was observed by a series of examinations with optical coherence tomography.

Results: All eyes showed a large chronic cystoid space in the fovea. Three eyes showed an epiretinal membrane and one eye showed traction of a posterior hyaloid membrane to the fovea. The chronic cystoid space changed into an LMH by rupture of its inner wall due to traction. After formation of the LMH, mean total foveal thickness decreased from 590 ± 131 μm to 95 ± 22 μm, which was equal to the thickness of the foveal photoreceptor layer before formation of the LMH (mean, 100 ± 23 μm). Visual acuity did not change substantially from before to after formation of the LMH.

Conclusions: Chronic CME associated with RVO can transform into an LMH by rupture of the inner wall of the foveal cystoid space. While this transformation is accompanied by a substantial reduction in macular thickness, it does not lead to change in visual function.

Key words: cystoid macular edema; lamellar macular hole; optical coherence tomography; retinal vein occlusion

Introduction

Cystoid macula edema (CME) is the most common vision-threatening complication associated with retinal vein occlusion (RVO) [1-3]. To date, various treatments have been reported to reduce macular edema from RVO, including grid laser photocoagulation [1, 4-6], pars plana vitrectomy combined with internal limiting membrane peeling [7], and intravitreal injection of triamcinolone acetonide [8-11] or bevacizumab [12]. In spite of these treatments, however, some patients have persistent CME, and never achieve full visual recovery [13].

A lamellar macular hole (LMH) is occasionally seen in eyes with old RVO [14]. Using only fundus examination, in many cases it is difficult to distinguish the LMH seen associated with old RVO from chronic CME [15]. So far, very limited information is available on the pathogenesis of LMH associated with RVO, or on its clinical significance [15, 16]. Based on histopathologic specimens, Gass suggested that LMH formation may be related to CME and epiretinal membrane (ERM) [17]. Recent technological advances in optical coherence tomography (OCT) allow a more detailed observation of CME and contribute to the elucidation of the pathomorphology of this condition without entailing histopathologic methods [18, 19]. Herein, with the use of successive examinations by OCT, we report four cases of spontaneous LMH formation that occurred in eyes with chronic CME associated with RVO.

Material and Methods

In the current study, we retrospectively reviewed the medical records of four eyes of four patients with chronic CME associated with RVO, in whom OCT examinations showed transformation of the cystoid space to an LMH. Two eyes had branch retinal vein occlusion (BRVO) and two eyes had central retinal vein occlusion (CRVO). All eyes included in this study had failed to respond to medical or to surgical treatment, including intravitreal injections of triamcinolone acetonide and bevacizumab, focal laser or panretinal photocoagulation, or pars plana vitrectomy. For each patient, a comprehensive medical interview was conducted regarding the presence of systemic diseases such as diabetes mellitus, hypertension, and hyperlipemia. Each patient underwent a comprehensive ophthalmologic examination, including determination of best-corrected visual acuity, testing of intraocular pressure, indirect ophthalmoscopy, slitlamp biomicroscopy with a contact lens, fundus photography, fluorescein angiography, and OCT. Visual acuity was measured with a Landolt chart. OCT scanning was performed using time-domain OCT (Stratus OCT3000, Carl Zeiss, Dublin, CA) or spectral-domain OCT (3DOCT-1000, Topcon, Tokyo, Japan, Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany). Using these OCT images, we measured total foveal thickness and thickness of the foveal photoreceptor layer. Total foveal thickness was defined as the distance between the vitreoretinal interface and retinal pigment epithelium in the fovea. Thickness of the foveal photoreceptor layer was defined as distance between the posterior surface of the cystoid space and retinal pigment epithelium in the fovea. This study was performed according to the tenets of the Declaration of Helsinki; for this retrospective study,

Institutional Review Board/Ethics Committee approval was not required.

Results

In the current study, four eyes of four patients (two men and two women) with chronic macular edema associated with RVO, ranging in age from 66 to 74 years (median, 70.5 years), were examined. Table 1 shows the characteristics of patients who were eligible for inclusion in this study. At the initial visit, three eyes showed marked CME. One eye showed macular thickening without cystoid spaces. Total foveal thickness at the initial visit ranged from 385 μm to 986 μm (mean, 698 ± 256 μm). Best corrected visual acuity at the initial visit ranged from 0.02 to 0.3 (median, 0.125). While one eye did not have any surgical treatment, the remaining three eyes had undergone various treatments for the macular edema. The two patients with CRVO had undergone panretinal photocoagulation, and one of the patients with BRVO had undergone focal photocoagulation to the affected area. Three patients had undergone pars plana vitrectomy to remove either an ERM or posterior hyaloid membrane.

In spite of the various types of treatment, all four eyes in the current study had chronic CME before formation of the LMH. Three patients had an ERM involving the foveal cystoid space, and one patient showed traction of the posterior hyaloid membrane to the fovea. OCT examinations revealed transformation of the foveal cystoid space to an LMH (Figs. 1-4). No patient, however, noticed a change in visual function during this transformation. The inner wall of the foveal cystoid space appeared to rupture with increased traction, and, after formation of the LMH, numerous cystoid spaces remained visible in parafoveal and extrafoveal locations. After formation of the LMH, the mean total foveal thickness decreased from 590 ± 131

μm to 95 ± 22 μm, which was equivalent to thickness of the foveal photoreceptor layer before formation of the LMH (mean, 100 ± 23 μm). Even the more precise OCT examinations showed no change in structure of the foveal photoreceptor layer, which was the base of the LMH. The mean duration from the occurrence of RVO to the detection of the LMH was 43.3 ± 31.6 months. Median visual acuity before and after detection of the LMH was 0.15 and 0.175, so visual acuity was essentially unchanged between before LMH formation and after LMH formation.

Case reports

Case 1.

A 66-year-old woman visited our clinic with a visual disturbance of the left eye (0.3 OS). At the initial visit, she had a retinal hemorrhage associated with BRVO, as well as marked macular edema with a large cystoid space beneath the fovea, which was 623 μm in thickness (Fig. 1a). Detachment of the posterior hyaloid membrane was not seen. She refused all surgical treatment and had follow-up examinations for only the persistent CME. At 17 months after the initial visit, she still showed chronic CME in the left eye; total foveal thickness was now 755 μm and thickness of the foveal photoreceptor layer was 74 μm (Fig. 1b). OCT revealed the posterior hyaloid membrane, which was attached to the fovea, and the inner wall of the foveal cystoid space, which seemed to be being torn off by traction of this posterior hyaloid membrane. Visual acuity remained 0.5 in the left eye. At 32 months, however, OCT showed a complete LMH just beneath the fovea (Fig. 1c). The extrafoveal cystoid spaces were still seen primarily in the outer plexiform layer. Foveal thickness

had decreased to 78 µm, although visual acuity in the left eye remained at 0.5.

Case 2.

A 73-year-old man visited our clinic with a sudden decrease of visual acuity in the left eye (0.02 OS). Examination of this eye showed an extensive retinal hemorrhage with severe macular edema associated with CRVO; foveal thickness was 986 µm. Panretinal photocoagulation was performed to the extensive nonperfused area of the left eye. Eight weeks after this initial visit for treatment of the macular edema, he received an intravitreal injection of bevacizumab, after which, to remove the thick ERM, pars plana vitrectomy with ERM peeling was performed. At 31 months after the initial visit, he had persistent CME with a recurrent ERM. Visual acuity in the left eye was 0.08. Total foveal thickness was 436 µm and thickness of the foveal photoreceptor layer was 129 µm (Fig. 2a). At 37 months after the first visit, OCT showed a marked decrease in foveal thickness. The inner wall of the foveal cystoid space was not seen but a complete LMH was noted at the centre of the fovea (Fig. 2b). There was no remarkable change of the photoreceptor layer beneath the fovea but foveal thickness had decreased to 110 µm; visual acuity was essentially unchanged at 0.07 OS.

Case 3.

A 68-year-old woman was seen in our clinic with decreased visual acuity in the right eye (0.1 OD). She showed extensive retinal hemorrhage with severe macular edema associated with CRVO in the right eye. Total foveal thickness was 796 µm.

edema associated with BRVO; foveal thickness was 986 µm. With pars plana vitrectomy and laser photocoagulation to the affected retina, macular edema was resolved and visual acuity recovered to 0.5 OD. Six years later, he had visual disturbance due to BRVO in the right eye (0.2 OD). He had a retinal hemorrhage associated with BRVO, as well as marked macular edema with large foveal cystoid spaces with fine ERM in the right eye. Total foveal thickness was 596 µm and thickness of the foveal photoreceptor layer was 98 µm (Fig. 4a). At 89 months after the first visit, OCT showed a marked decrease in foveal thickness. The inner wall of the foveal cystoid space was not seen but a complete LMH was noted (Fig. 4b). There was no remarkable change of the photoreceptor layer beneath the fovea but foveal thickness had decreased to 116 µm; visual acuity was unchanged at 0.2 OD.

Discussion

LMH is defined as a partial defect of the inner retinal tissue in the fovea.[20] Despite the original description of LMH by Gass [17], the process of LMH formation was not completely understood until recent reports of studies that used OCT [21-26], With the precise observations by OCT, LMH can be classified into three distinct categories: 1) associated with ERM, 2) secondary to CME, and 3) associated with acute posterior vitreous detachment [27]. In the current study, we showed transformation into LMH of a chronic foveal cystoid space that was associated with RVO. Three of our patients showed an ERM and the other patient showed traction of the posterior hyaloid membrane to the fovea. In the case of RVO, rupture of the inner wall of the foveal cystoid space due to traction caused formation of the LMH. Recently, Unoki et al.[28] reported similar findings in eyes with diabetic retinopathy. Using a computerized search of MEDLINE, however, we could find no reference to the course of transformation into LMH of the cystoid space associated with RVO [16]. In one eye with CRVO, after formation of the LMH from chronic CME, the LMH was spontaneously closed and recurrent CME led to another LMH, although the precise mechanism is uncertain.

Once there was formation of LMH in our patients, the foveal cystoid space disappeared and the total foveal thickness decreased to less than physiologic levels. Unless we recognize the formation of LMH, we may think that the CME has healed completely. However, no eye showed a change in visual acuity during this transformation, and, furthermore, the extrafoveal cystoid spaces remained after transformation. Recently, several reports have shown the efficacy of pars plana

vitrectomy for LMH associated with ERM [29-32]. However, It is still uncertain whether additional treatment, such as pars plana vitrectomy combined with internal limited membrane peeling, is necessary for the type of LMH seen in our patients. In these patients, each of whom had an old RVO, the recovery of visual function may be limited, even with pars plana vitrectomy, because of damage to the foveal photoreceptor cells caused by the long-standing CME.

Recently, integrity of the foveal photoreceptor layer, especially its outer aspect, has been suggested to be essential to visual acuity [33]. In eyes with resolved macular edema associated with BRVO, Murakami et al.[34] suggested that, to achieve good visual recovery, a simple reduction in foveal thickness is insufficient, and that restoration of structure of the photoreceptors to a more physiologic condition is needed. In addition, Ota et al.[13] reported that thickness of the foveal photoreceptor layer is correlated closely with visual function in eyes with persistent or recurrent CME associated with BRVO. Even in eyes with a large cystoid space in the fovea, if the foveal outer photoreceptor layer beneath the cystoid space is intact, visual acuity can be preserved [13]. In the current study, mean total foveal thickness after the formation of LMH was equivalent to the thickness of the foveal photoreceptor layer before transformation. In addition, even the more precise OCT examinations showed no remarkable change in structure of the foveal photoreceptor layer. A previous report by Ota et al.[13] may explain our finding that visual acuity did not change during the formation of LMH.

From our findings, we can say that the inner wall of the foveal cystoid space plays a minor role in visual function. Singh et al.[35] have reported that, although

surgical puncture of the CME caused the structural cystoid changes of the retina to resolve, it failed to improve visual acuity. Our findings in the current study may explain the efficacy of puncture of the CME in eyes with RVO, but to treat CME associated with long-standing RVO, it may be essential to retain integrity of the foveal photoreceptor layer.

Limitations of the current study are its retrospective nature and small number of cases. Although LMH is a rare complication of old RVO, we have shown that chronic CME in RVO can, in fact, transform into LMH. In the formation of the LMH, traction of posterior hyaloid membrane or ERM causes rupture of the inner wall of the foveal cystoid space. Although this transformation is accompanied by a substantial reduction in macular thickness, it does not necessarily lead to change in visual function. In addition, the current findings support the importance of the foveal photoreceptor layer in chronic CME that accompanies RVO, although the perfusion status around the fovea was not evaluated sufficiently.

She was treated with panretinal photocoagulation to the extensive nonperfused area of the right eye. In spite of the various treatments for the CME (an intravitreal injection of tissue plasminogen activator, an intravitreal injection triamcinolone acetonide, and pars plana vitrectomy), it did not resolve. At 28 months after the initial visit, she showed a chronic large cystoid space beneath the fovea with an ERM that involved the fovea. Visual acuity was 0.1 in the right eye. Total foveal thickness was 572 μm and thickness of the foveal photoreceptor layer was 99 μm (Fig. 3a). At 30 months, OCT revealed formation of the LMH. The inner wall of the foveal cystoid space was not seen, but extrafoveal cystoid spaces were still visible in the inner nuclear and outer plexiform layers. Foveal thickness decreased to 74 μm, although visual acuity was unchanged (0.15 OD) (Fig. 3b). After three months (33 months after the initial visit), OCT showed a recurrence of the large foveal cystoid space; foveal thickness had increased to 660 μm and thickness of the foveal photoreceptor layer beneath the foveal cystoid space was 95 μm (Fig. 3c). An ERM was still seen in the macular area. Three years after the recurrence of CME, OCT showed a recurrent LMH. No remarkable change was detected in the photoreceptor layer beneath the fovea but foveal thickness had decreased to 112 μm; visual acuity was essentially unchanged (0.1 OD) (Fig. 3d). ERM in the macular area showed no change during the reformation of LMH.

Case 4.

A 74-year-old man visited our clinic with a decrease of visual acuity in the right eye (0.15 OD). Examination of this eye showed retinal hemorrhage with severe macular

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Figure legends

Figure 1. Lamellar macular hole formation by traction of the posterior hyaloid membrane to the chronic foveal cystoid space associated with branch retinal vein occlusion. Horizontal (left) and vertical (right) optical coherence tomographic images centered on the fovea. (**a**) At 17 months after the initial visit, chronic cystoid edema is seen. Total foveal thickness at this time was 755 μm and thickness of the foveal photoreceptor layer was 74 μm. (**b**) The inner wall of the foveal cystoid space seems to be being torn off by traction of the posterior hyaloid membrane. Visual acuity was still 0.5. (**c**) A lamellar macular hole has formed just beneath the fovea. Extrafoveal cystoid spaces are still seen in the outer plexiform layer. Foveal thickness decreased to 78 μm but visual acuity remained at 0.5.

Figure 2. Lamellar macular hole formation by traction of the epiretinal membrane to the foveal cystoid space associated with central retinal vein occlusion. Horizontal (upper) and vertical (lower) optical coherence tomographic images centered on the fovea. (**a**) At 31 months after the initial visit, a large foveal cystoid space is seen, as is a recurrent epiretinal membrane. Visual acuity was 0.08. Total foveal thickness was 436 μm and thickness of the foveal photoreceptor layer was 129 μm. (**b**) A lamellar macular hole has been formed by the defect of the inner wall of the foveal cystoid space. No remarkable change is detected in the photoreceptor layer beneath the fovea. Foveal thickness decreased to 110 μm but visual acuity was essentially unchanged (0.07 OS).

Figure 3. Recurrent lamellar macular hole formation in the foveal cystoid space associated with central retinal vein occlusion. Horizontal (left) and vertical (right) optical coherence tomographic images centered on the fovea. (**a**) At 28 months after the initial visit, a chronic large cystoid space is seen beneath the fovea along with an epiretinal membrane that involves the fovea. Visual acuity was 0.1. Total foveal thickness was 572 µm and thickness of the foveal photoreceptor layer was 99 µm. (**b**) A lamellar macular hole is now seen in the foveal cystoid space. Surrounding extrafoveal cystoid spaces remain visible in the inner nuclear and outer plexiform layers. Foveal thickness decreased to 74 µm but visual acuity was unchanged (0.15 OD). (**c**) Three months later, a large foveal cystoid space has recurred. Foveal thickness increased to 660 µm and thickness of the foveal photoreceptor layer just beneath the foveal cystoid space was 95 µm at that time. A thin epiretinal membrane is seen in the macular area. (**d**) Three years after recurrence of the foveal cystoid space, recurrence of a lamellar macular hole is seen. Foveal thickness decreased to 112 µm but visual acuity was essentially unchanged (0.1 OD).

Figure 4.

Lamellar macular hole formation associated with recurred branch retinal vein occlusion. Vertical optical coherence tomographic images centered on the fovea. (**a**) At 76 months after the initial visit, large cystoid spaces are seen beneath the fovea along with an epiretinal membrane. Visual acuity was 0.2. Total foveal thickness was 596 µm and thickness of the foveal photoreceptor layer was 98 µm. (**b**) A lamellar macular hole has been formed by the defect of the inner wall of the foveal

cystoid space. No remarkable change is detected in the photoreceptor layer beneath the fovea. Foveal thickness decreased to 116 μm but visual acuity was unchanged (0.2 OD).

Table 1.

Table 1. Patient characteristics before and after formation of the LMH associated with RVO

			Initial visit			Before formation of the LMH				After formation of the LMH		
Patient	Age (years) /gender	Type of RVO	Visual acuity	Total foveal thickness (μm)	Treatments	Visual acuity	Total foveal thickness (μm)	Thickness of foveal photoreceptor layer (μm)	Duration to LMH formation (month)	Visual acuity	Total foveal thickness (μm)	Follow-up (month)
1	66/F	BRVO	0.3	623	None	0.5	755	74	17	0.5	78	39
2	73/M	CRVO	0.02	385	PPV, PRP, an intravitreal injection of bevacizumab	0.08	436	129	37	0.07	110	37
3	68/F	CRVO	0.1	796	PPV, PRP, an intravitreal injection of t-PA, an intravitreal injection of TA	0.1	572	99	30	0.15	74	-
			-	-		0.1	660	97	69	0.1	112	96
4	74/M	BRVO	0.15	986	PPV, focal PC	0.2	596	98	89	0.2	116	92

LMH, lamellar macular hole; RVO, retinal vein occlusion; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; PPV, pars plana vitrectomy; PRP, panretinal photocoagulation; t-PA, tissue plasminogen activator; TA, triamcinolone acetonide; PC, photocoagulation.

Visual acuity was measured with a Landolt chart.

Figure 1.

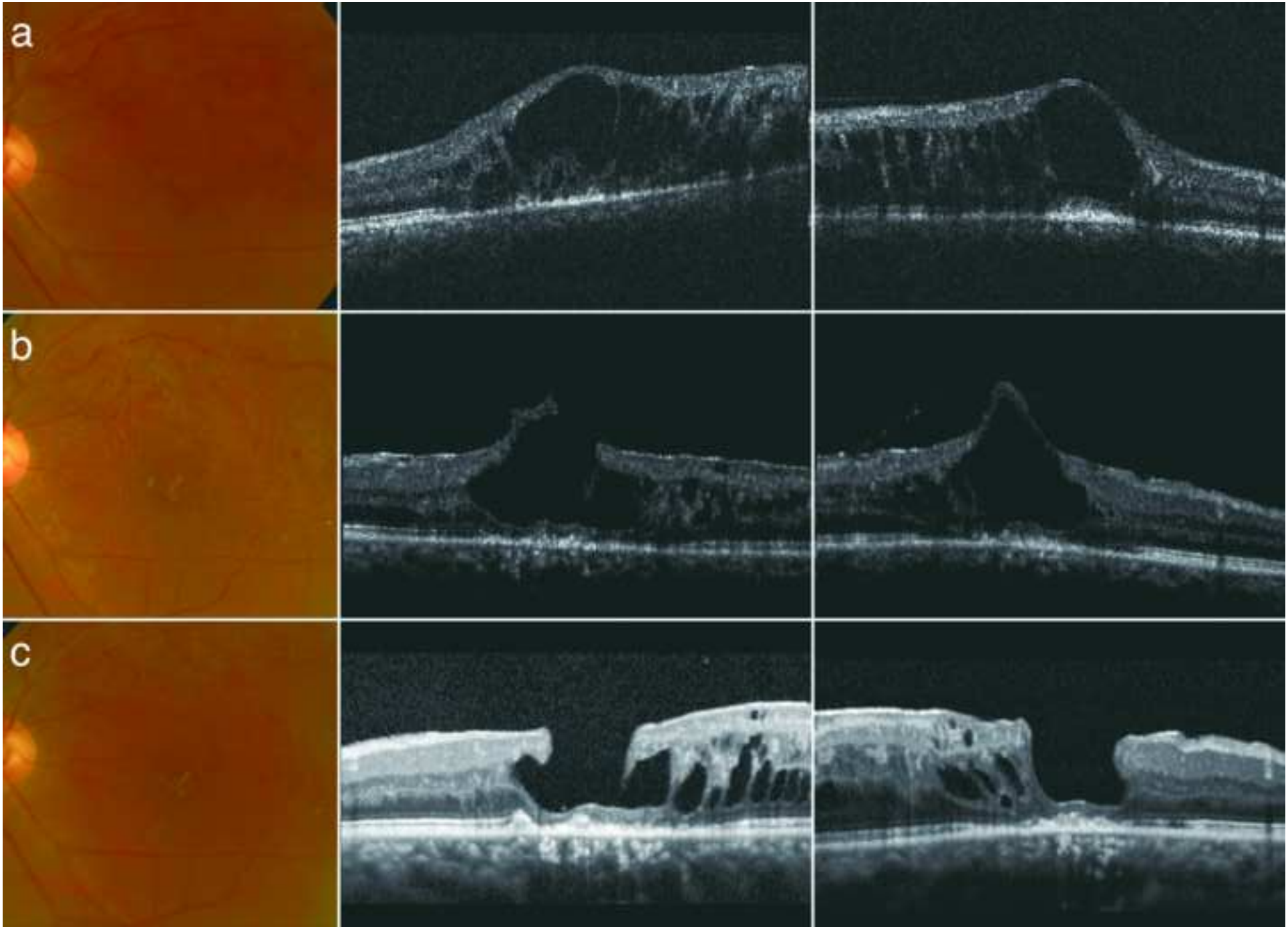

Figure 2.

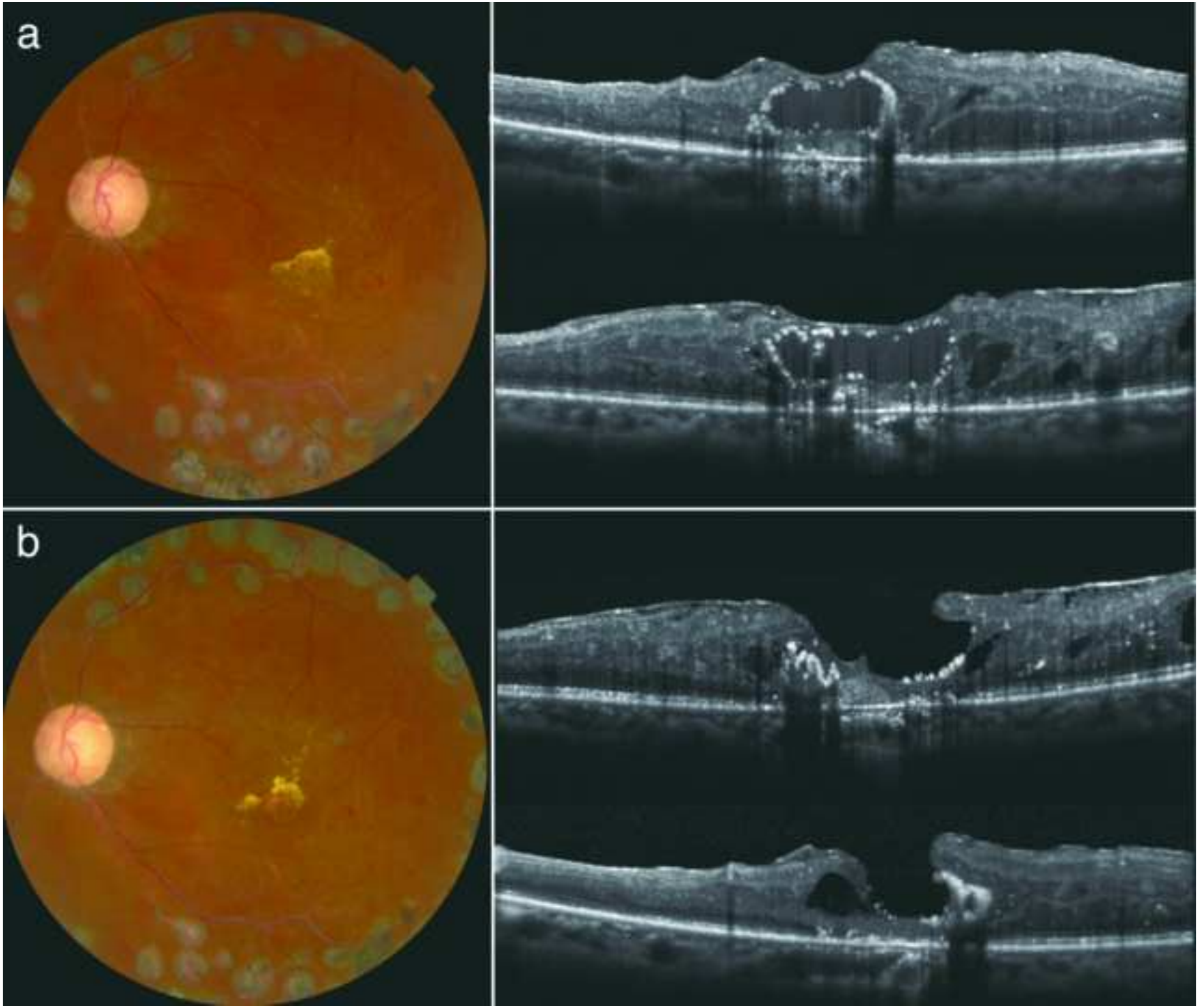

Figure 3.

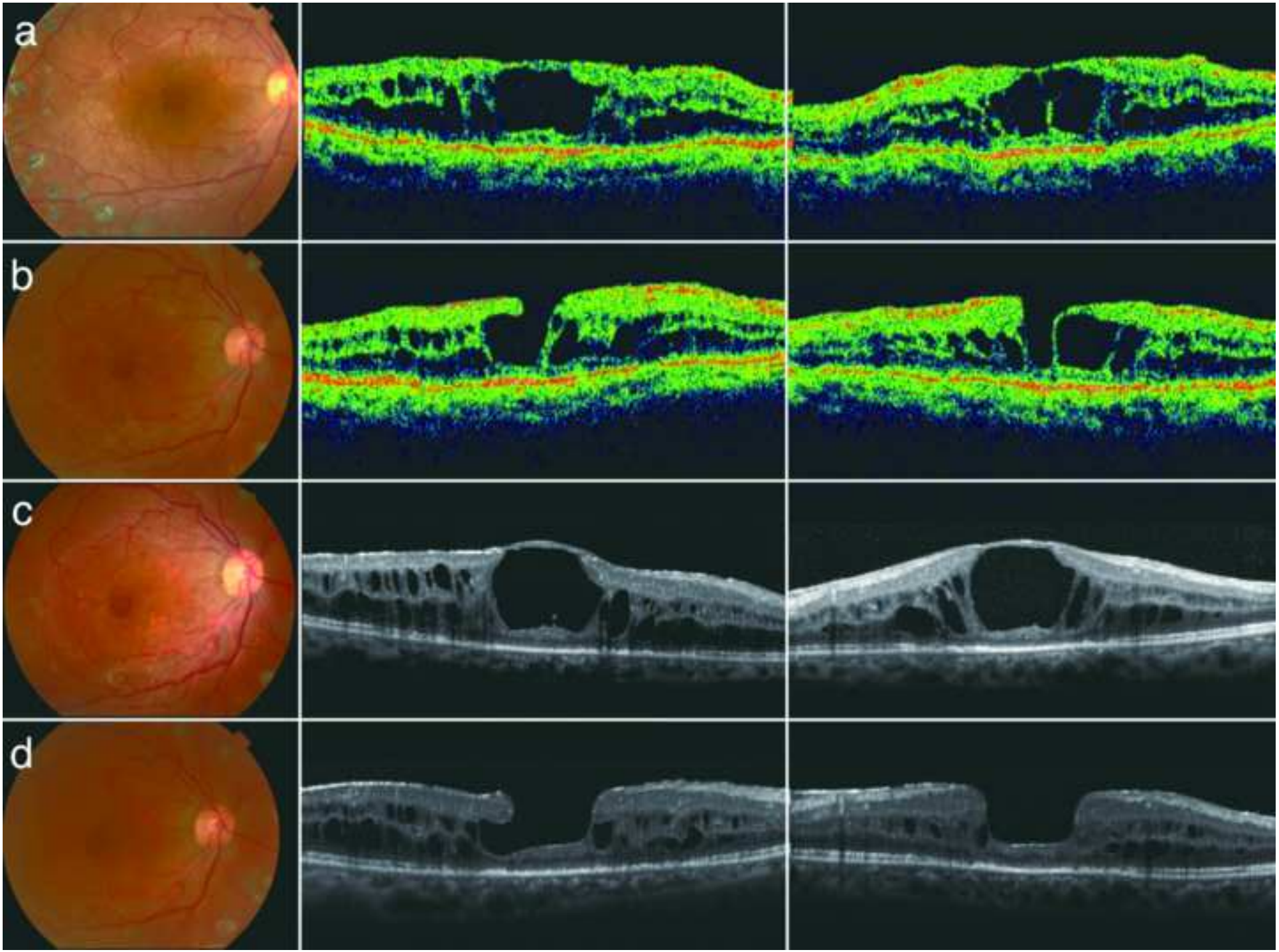

Figure 4.