

Title page

Title: Branch retinal vein occlusion associated subretinal hemorrhage

Yuki Muraoka · Akitaka Tsujikawa · Tomoaki Murakami · Ken Ogino · Kazuaki Miyamoto ·
Nagahisa Yoshimura

Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of
Medicine, Kyoto, Japan.

Running title: BRVO associated subretinal hemorrhage

(✉) Akitaka Tsujikawa, MD, Department of Ophthalmology, Kyoto University Graduate School
of Medicine, Sakyo-ku, Kyoto 606-8507, Japan.
fax: +81-75-752-0933; tel: +81-75-751-3260; e-mail: tujikawa@kuhp.kyoto-u.ac.jp

Abstract

Purpose To study the pathomorphology of subretinal hemorrhage (SRH) seen in eyes with branch retinal vein occlusion (BRVO) and its association with visual prognosis.

Methods We reviewed retrospectively 42 consecutive patients (42 eyes) with BRVO that affected the fovea. Retinal structural changes were examined by spectral domain optical coherence tomography (SD-OCT).

Results On SD-OCT sections, serous retinal detachment was seen at the fovea in 35 eyes, 18 of which accompanied foveal SRH. While initial detection of foveal SRH had no correlation with initial visual acuity (VA), it was correlated with poorer final VA ($r = 0.361$, $P = 0.019$). Our patients were classified into two groups by the initial detection of foveal SRH, and initial VA was not different between these two groups. At the final examination, damaged lengths in the foveal photoreceptor layer were significantly longer in the SRH positive group than those in the SRH negative group ($P = 0.004$), and final VA in the SRH positive group was significantly worse than that in the SRH negative group ($P = 0.019$).

Conclusion Foveal SRH is not an uncommon feature in BRVO and may cause subsequent damage to the foveal photoreceptor layer, resulting in poor visual function.

Key words Branch retinal vein occlusion • Subretinal hemorrhage • Photoreceptor damage • Spectral-domain optical coherence tomography.

1 Introduction

2 Branch retinal vein occlusion (BRVO), one of the most common vascular occlusive
3 diseases of the retina [1-3], is caused by a retinal circulatory disturbance in a main trunk of the
4 retinal veins. Acute BRVO is characterized by flame-shaped retinal hemorrhage and venous
5 engorgement in the affected retina, often with macular edema. In eyes with acute BRVO, visual
6 acuity (VA) often decreases because of the macular edema, which can be clinically diagnosed
7 based on fundus examination, fluorescein angiography and/or optical coherence tomography
8 (OCT). A number of treatments are now used for the regression of the macular edema, including
9 intravitreal injections of anti-vascular endothelial growth factor agents [4-7].

10 Recent technologic advances in OCT revealed that the retinal morphological changes in
11 BRVO exist not only in the inner retina but in the outer aspects, occasionally even in the
12 subretinal spaces [8-12]. Yamaike et al. [10] report that macular edema associated with acute
13 BRVO consists of cystoid spaces in various retinal layers and marked retinal swelling especially
14 in the retinal outer layers. Serous retinal detachment (SRD) is also often accompanied at the
15 BRVO-affected fovea [8, 11, 13, 14]. In addition, recent OCT studies reveal that visual function
16 correlates with the integrity of the foveal photoreceptor layer, i.e., the junction between inner and
17 outer segments of the photoreceptors (IS/OS) [15-19], and the external limiting membrane
18 (ELM) [20, 21]. Murakami et al. [22] report that in resolved macular edema with BRVO, the
19 condition of the foveal IS/OS was correlated with VA. However, there is little information on
20 which pathology in acute BRVO determines the integrity in foveal photoreceptors after the
21 resolution of the retinal hemorrhage and retinal thickening [23].

22 With detailed fundus examination by slitlamp biomicroscopy, clinicians sometimes find the
23 BRVO-affected eyes showing hemorrhage within foveal cystoid spaces and/or subretinal space
24 [8, 9, 11]. In eyes with BRVO, while the hemorrhage is rarely seen in retinal inner surface at

foveal center, subretinal hemorrhage (SRH) is located just at the fovea, which may cause damage to the foveal photoreceptors [8, 9, 24]. However, the reports about characteristic and clinical relevance of BRVO-induced SRH are scant [23, 24]. In the current study, we elucidated the clinical characteristics of SRH in eyes with BRVO and their correlations with the morphologic and functional changes of foveal photoreceptors, by examining OCT images captured between the acute and chronic phases.

Subjects and Methods

For this observational case study, we reviewed retrospectively the medical records of 42 consecutive patients (42 eyes) with acute BRVO who were seen by members of the Department of Ophthalmology at Kyoto University Hospital between June 2008 and January 2011. Inclusion criteria included (1) symptomatic BRVO, in which retinal hemorrhage and retinal edema extended to the macula, (2) foveal thickness measured by SD-OCT greater than 250 μm at initial visit, (3) duration of symptoms until initial examination less than 3 months, and, (4) a minimum follow-up of 6 months after the initial visit. The diagnosis of BRVO was based on fundus examination and fluorescein angiography findings by two retina specialists (AT, TM). Eyes with central retinal vein occlusion or hemi-central retinal vein occlusion were excluded from the current study. Eyes with co-existing ocular disease (i.e., epiretinal membrane, glaucoma, diabetic retinopathy or senile cataract that resulted in poor quality SD-OCT images) and eyes that had been treated previously for BRVO were also excluded. Of the 42 eyes included in the present study, 12 were treated with grid laser photocoagulation, 5 underwent pars plana vitrectomy for treatment of their macular edema during follow-up, and the remaining 25 eyes received no treatment. The current study was approved by the Institutional Review Board at Kyoto University Graduate School of Medicine and adhered to the tenets of the Declaration of Helsinki.

At the initial examination, each patient underwent a comprehensive ophthalmologic examination, which included measurement of best-corrected VA with a Landolt chart, determination of intraocular pressure, indirect ophthalmoscopy, slitlamp biomicroscopy with a non-contact lens, and SD-OCT examination. To assess retinal perfusion status, each patient underwent fluorescein angiography with a confocal laser scanning system (HRA-2, Heidelberg Engineering, Heidelberg, Germany). Eyes with BRVO were classified as ischemic when the area of nonperfusion was greater than 5-disc diameters in size. In addition, the entire macular region

1 was examined with Spectralis HRA+OCT (Heidelberg Engineering).

2 Using the initial SD-OCT images, we performed quantitative measurements and
3 morphologic evaluations at the fovea. Foveal thickness was defined as the mean distance between
4 the vitreoretinal interface and retinal pigment epithelium within a circle measuring 1 mm in
5 diameter centered on the fovea. Using this data, the cystoid spaces, SRD and SRH of each patient
6 were judged to have been either within or without the foveal area. Whenever foveal cystoid
7 spaces were seen, they were examined to establish whether they were hemorrhaging. To assess
8 the integrity of the foveal outer retina, we examined the condition of the ELM line and of the
9 IS/OS line in the foveal area. Evaluations of the foveal ELM and IS/OS were performed within
10 the central 1-mm area of fovea using gray-scale vertical OCT images. The status of the foveal
11 ELM line and of the IS/OS line were classified as being complete if the complete line could be
12 detected in the central 1-mm area of the fovea, or as being incomplete if not.

13 Each patient underwent a second comprehensive ophthalmologic examination, including
14 measurement of best-corrected VA, indirect ophthalmoscopy, slitlamp biomicroscopy with a
15 non-contact lens, and OCT examination with the Spectralis HRA+OCT. Fluorescein angiography
16 was performed if deemed necessary. Using SD-OCT images at the final examination of each
17 follow-up period (14.8 ± 5.4 months, 6-28 months), we performed the same quantitative
18 measurements and morphologic evaluations within the foveal area as had been performed
19 previously. In addition, we measured the defect lengths seen in the ELM line or in the IS/OS line
20 within the central 1-mm area on vertical and horizontal SD-OCT scans; this was done with the
21 software that was built into the Spectralis HRA+OCT.

22 Statistical analysis was performed using PASW Statistics version 18.0 (SPSS, Chicago, IL,
23 USA). All values are presented as mean $\pm$ standard deviation. For statistical analysis, VA
24 measured with a Landolt chart was converted to a logarithm of the minimum angle of resolution

(logMAR). Analysis of the two groups was done using the Student's *t* test, and bivariate relationships were analyzed using the Pearson's correlation coefficient. A stepwise forward multivariate linear regression analysis was performed to evaluate the contribution made by each initial factor to the final VA. A *P* value of less than 0.05 was considered to be statistically significant.

Results

In the current study, 42 eyes of 42 patients (23 women and 19 men) with BRVO, ranging in age from 42 to 83 years (64.9 ± 10.1 years) were examined. Table 1 shows initial measurements of all patients who were eligible for inclusion in this study.

At the initial visits, all eyes showed intraretinal hemorrhage and macular thickening; mean foveal thickness was 557.8 ± 156.8 μm . Of the 42 eyes, cystoid spaces were seen in 34 eyes, SRD at the fovea in 35 eyes. Fundus examination revealed hemorrhage within subretinal spaces and/or foveal cystoid spaces in some eyes, this was detected more sensitively on OCT images. On OCT sections, 19 of the 34 eyes had foveal cystoid spaces with hemorrhage within these spaces; hemorrhage within the foveal cystoid spaces often made a niveau formation and occasionally appeared as amorphous hyperreflectivity (Fig. 1). Eighteen of the 35 eyes with foveal SRD accompanied SRH within the subretinal space; the SRH appeared as homogenous hyper-, or, as amorphous mild to moderate hyperreflectivity (Fig. 1). Sequential OCT sections of the affected fovea demonstrated that the hemorrhage within foveal cystoid spaces connected to the SRH through the external boundary of the retina in some eyes (Fig. 2). Of the 18 eyes with SRH at the fovea, 16 showed hemorrhage within the foveal cystoid spaces.

Table 2 shows the association of initial VA with other measurements at the initial visits.

At the initial examination, foveal ELM was completely seen in 14 and IS/OS, in 9 eyes. Although

the detection of foveal IS/OS line showed only a marginal correlation with initial VA ($r = 0.261$, $P = 0.095$), the detection rate of foveal ELM showed a more obvious correlation with initial VA ($r = 0.366$, $P = 0.017$).

At the final visits, VA had improved significantly to 0.21 ± 0.33 ($P = 0.002$), and macular edema was substantially reduced; foveal thickness was decreased to $365.5 \pm 137.2 \mu\text{m}$ (range 227--791 μm) ($P < 0.001$). In parallel with resolution of the macular edema, integrity of the foveal photoreceptor layers got to be recovered; the ELM and IS/OS lines at the fovea were completely detected in 21, and 17 eyes, respectively. Table 3 shows association of final VA with the other measurements at the final visits. Better final VA was linearly correlated with less foveal thickness ($r = 0.358$, $P = 0.027$), more detection rate of foveal ELM ($r = 0.419$, $P = 0.006$) and IS/OS line ($r = 0.565$, $P = 0.002$). Furthermore, the defect lengths in the ELM and IS/OS lines were correlated most closely with poor final VA ($r = 0.532$, $P < 0.001$; $r = 0.543$, $P < 0.001$).

Table 4 shows associations of final VA with the initial visits-measurements. Five factors at the initial examinations including foveal thickness ($r = 0.496$, $P < 0.001$) and presence of hemorrhage within the foveal cystoid spaces ($r = 0.459$, $P = 0.002$), and SRH ($r = 0.361$, $P = .019$) were significantly correlated with poorer final VA by simple regression analysis. We thus investigated the association of these 5 independent factors with the final VA by multiple regression analysis. Initial foveal thickness was closely ($\beta = 0.374$, $P = 0.006$), and initial detection of foveal SRH was marginally correlated with the final VA ($\beta = 0.279$, $P = 0.061$).

Therefore, our patients were classified into one of two groups depending on whether foveal SRH was detected at the initial examination, or not (Table 5). Although initial VA was not different between the two groups ($P = 0.490$), final VA (0.37 ± 0.35 , range -0.08--1.10) in the SRH positive group was significantly worse than that (0.14 ± 0.27 , range -0.18--0.30) in the SRH negative group ($P = 0.019$). In addition, the vertical and horizontal defect lengths in the foveal

IS/OS line of the SRH positive group were significantly longer ($P = 0.004$) than those of the SRH negative group, $P = 0.028$). In the foveal ELM, the horizontal defect length was longer than in the SRH negative group ($P = 0.017$) (Table 5, Fig. 3).

Discussion

A prominent feature in acute BRVO is the intraretinal hemorrhage. However, although some eyes with BRVO hemorrhage within the subretinal or cystoid spaces [8, 9, 11] information on the nature of these, or on their clinical relevance is limited [25]. Using of OCT, Spaide et al.[8] report two cases of BRVO with SRH, and Tsujikawa et al.[11] report other cases that showed hemorrhage within the macular cystoid spaces. However, the association of the hemorrhage with visual function is not reported. In the current study, detailed OCT examination revealed that, in acute BRVO, hemorrhage like this is not uncommon . Of our 42 patients with BRVO, 19 had hemorrhage in the foveal cystoid space and 18 had in the subretinal space at the fovea. In addition, initial detection of these were correlated closely with final VA.

In acute BRVO, intravascular pressure within the affected retinal veins and capillaries is increased, which leads to leakage and hemorrhage from the affected capillaries. Eyes with BRVO often had large foveal cystoid spaces with surrounding small cystoid spaces in the inner nuclear layer and outer plexiform layer, in many cases with SRD at the fovea [10, 11]. In the present study, of 18 eyes with foveal SRH, 16 showed hemorrhage within the foveal cystoid spaces. On OCT sections, hemorrhage within the foveal cystoid space sometimes connected to underlying SRH through the external boundary of the retina. It is possible that hemorrhage from the affected capillaries accumulates within the foveal cystoid spaces, and then flows into the subretinal space through the base of the cystoid space.

In the current study, initial detection of hemorrhage within the subretinal and/or foveal cystoid spaces had no correlation with the initial VA. It is well known that both submacular hemorrhage in age-related macular degeneration [26-29] and in retinal macroaneurysm [27, 30] often cause an immediate decrease in VA. However, even if the hemorrhage associated with BRVO is at the fovea, it does not cause an immediate severe decrease in visual function at the

fovea. In acute BRVO, because the foveal SRH is small and usually exists with some subretinal fluid, it may not block oxygen and nutrients from choroidal circulation and consequently not develop acute impairment of visual function. At the final examinations of the present study, the macular edema was substantially reduced and both SRD and SRH had been almost entirely absorbed. In parallel with the resolution of the macular edema, some eyes showed recovery in the integrity of foveal photoreceptor layers. The final conditions of the foveal ELM and the IS/OS lines were closely correlated with the final VA. Furthermore, the defect lengths in the ELM and IS/OS lines were most closely correlated with poor VA. Ojima et al.[31] report similar findings in eyes with resolved central serous chorioretinopathy. Eyes with a fine defect of the foveal IS/OS line usually achieved good VA after complete resolution of the SRD, whereas a severe defect of the foveal IS/OS lines often resulted in substantial visual impairment.

By simple regression analysis, hemorrhage within the foveal cystoid spaces ($r = 0.459$, $P = 0.002$) and foveal SRH ($r = 0.361$, $P = 0.019$) at the initial examination showed close correlations with poor final VA. Using multiple regression analysis, final VA showed only a marginal correlation with foveal SRH ($\beta = 0.160$, $P = 0.061$), and there was no correlation between final VA and hemorrhage within the foveal cystoid spaces ($\beta = 0.279$, $P = 0.302$). As mentioned above, because most eyes with foveal SRH also had some hemorrhage within the foveal cystoid spaces, these might be confounding factors. This may be explained by our hypothesis that hemorrhage from the affected retinal capillaries accumulates within the foveal cystoid spaces and subsequently flows into the subretinal space.

Because the multiple regression analysis suggested that foveal SRH is one of the factors that determines visual prognosis in acute BRVO, we separated our patients into two groups by initial detection or no detection of a foveal SRH. Eyes with SRH had a mean longer defect of the foveal IS/OS line and poorer final VA than eyes without SRH. Although foveal SRH was not

1 associated with acute impairment of foveal function, it seemed to cause chronic damage to the
2 overlying foveal photoreceptor layer, which resulted in the limited recovery of vision.

3 Previous experimental studies suggest several mechanisms by which SRH damaged the
4 overlying photoreceptor cells, i.e., clot retraction [32], iron toxicity [33-35] and blockage of
5 nutrients diffusion from the choroidal circulation [36]. The primary toxic agent released from
6 SRH is thought to be iron as the form of ferritin [37], and increased iron in the photoreceptor
7 outer segments is reported to exert a toxic effect by inducing oxidative stress to outer segment
8 lipids [38]. Another experimental study reports that fibrin made from the SRH interdigitated with
9 photoreceptor outer segments, and subsequently tore the inner and outer segment sheets out of
10 photoreceptors. In eyes with BRVO, foveal SRH may chronically damage overlying
11 photoreceptors, leading to decrease in central visual function even after resolution of the
12 hemorrhage.

13 Major limitations of the current study are its retrospective nature and small sample size.
14 In addition, the study compared OCT images only between the initial and final examinations.
15 There is also the possibility of effects of the treatment administered to the patients which may
16 induce a bias in the interpretation of data. Despite these shortcomings, we demonstrated that
17 foveal SRH is not uncommon in BRVO, and may cause subsequent damage to the foveal
18 photoreceptor layer, which results in poor visual function after resolution of the retinal edema and
19 retinal hemorrhage. However, prospective studies with larger sample size are necessary to avoid
20 treatments effects.

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Figure legends

Fig. 1 Hemorrhage within the foveal cystoid spaces and subretinal hemorrhage associated with branch retinal vein occlusion. **a** Magnified fundus photograph shows a retinal hemorrhage in the shape of meniscus beneath the fovea (arrowheads) (66-year-old woman, 0.4 OD). **b** In a vertical section through the fovea obtained with optical coherence tomography, this retinal hemorrhage shows a niveau formation within a large foveal cystoid space (short arrow). Subretinal hemorrhage is also seen under the fovea (long arrow). **c** Magnified fundus photograph shows superficial retinal hemorrhage with subretinal hemorrhage at the fovea (arrowheads) (76-year-old woman, 0.3 OS). **d** Vertical section through the fovea obtained with optical coherence tomography shows subretinal hemorrhage seen on the fundus photograph as intense homogenous hyperreflectivity (arrow) in the subretinal space. Yellow arrows show foveal center in each eye.

Fig. 2 Subretinal hemorrhage connected to hemorrhage within a foveal cystoid space (70-year-old man, 0.5 OS). Fundus photograph (**a**) and fluorescein angiogram (**b**) show the retinal hemorrhage associated with branch retinal vein occlusion. Oblique (**c**) and horizontal (**d**) sections obtained with optical coherence tomography along white arrows shown in the angiogram show hemorrhage within a foveal cystoid space (short arrows) and subretinal hemorrhage (long arrows). Subretinal hemorrhage appears to be connected to the hemorrhage within the foveal cystoid space through the external boundary of the neurosensory retina.

Fig. 3 Damage to the foveal outer retina associated with subretinal hemorrhage from branch retinal vein occlusion (53-year-old woman, 0.3 OS). **a** Initial fundus photograph shows superficial retinal hemorrhage associated with acute branch retinal vein occlusion. Neither

1 hemorrhage within the foveal cystoid space nor subretinal hemorrhage is obvious. **b** A vertical
2 section through the fovea obtained with optical coherence tomography (OCT) reveals
3 hemorrhage within the foveal cystoid space (short arrow) and subretinal hemorrhage (long arrow).
4 **c** Fundus photograph taken 16 months after initial examination shows complete absorbance of the
5 retinal hemorrhage (0.6 OS). Vertical **(d)** and horizontal **(e)** OCT sections through the fovea
6 confirms complete absorption of the macular edema, and the foveal outer retina appears to be
7 substantially degenerated: line of the external limiting membrane (ELM) and line of junction
8 between inner and outer segments of the photoreceptors (IS/OS) show focal defects in the foveal
9 area. *RPE* retinal pigment epithelium.

Table 1 Initial and Final Conditions of Eligible Patients with Branch Retinal Vein Occlusion

Age (years)	64.9 ± 10.1 (42--83)
Gender (women/men)	23/19
Duration of symptom until initial examination (weeks)	3.9 ± 2.9 (0.4--9.9)
Follow-up (months)	14.9 ± 5.4 (6--28)
Initial examination	
Visual acuity (logMAR)	0.44 ± 0.35 (0--1.22)
Foveal thickness (μm)	557.8 ± 156.8 (296--886)
Foveal cystoid spaces	34
Hemorrhage within foveal cystoid spaces	19
Foveal SRD	35
Foveal SRH	18
Status of foveal ELM (complete/incomplete)	14/28
Status of foveal IS/OS (complete/incomplete)	9/33
Retinal perfusion status (ischemic/non-ischemic)	28/14
Final examination	
Visual acuity (logMAR)	0.24 ± 0.33 (-0.18--1.1)
Foveal thickness (μm)	365.5 ± 137.2 (227--791)
Status of foveal ELM (complete/incomplete)	21/21
Status of foveal IS/OS (complete/incomplete)	17/25
Vertical defect length in foveal ELM (μm)	135.0 ± 195.4 (0--810)
Horizontal defect length in foveal ELM (μm)	183.4 ± 286.5 (0--1000)
Vertical defect length in foveal IS/OS (μm)	283.2 ± 312.8 (0--1000)
Horizontal defect length in foveal IS/OS (μm)	237.0 ± 299.6 (0--1000)

logMAR logarithm of the minimum angle of resolution, *SRD* serous retinal detachment, *SRH*

subretinal hemorrhage, *ELM* external limiting membrane, *IS/OS* junction between inner and outer segments of the photoreceptors.

Table 2 Association of Initial Visual Acuity with Other Measurements Obtained at Initial

Examination

	r	P-value
Age (years)	0.232	0.139
Duration of symptom (weeks)	0.088	0.580
Foveal thickness (μm)	0.206	0.202
Foveal cystoid spaces	0.152	0.338
Hemorrhage within foveal cystoid spaces	0.243	0.121
Foveal SRD	0.109	0.454
Foveal SRH	0.109	0.490
Status of foveal ELM	0.366	0.017
Status of foveal IS/OS	0.261	0.095
Retinal perfusion status	0.093	0.561

SRD serous retinal detachment, *SRH* subretinal hemorrhage, *ELM* external limiting

membrane, *IS/OS* junction between inner and outer segments of the photoreceptors.

Table 3 Association of Final Visual Acuity with Other Measurements Obtained at Final

Examination

	r	P-value
Age (years)	0.359	0.020
Duration from initial symptoms (months)	-0.059	0.712
Foveal thickness (μm)	0.358	0.027
Status of foveal ELM	0.419	0.006
Status of foveal IS/OS	0.465	0.002
Vertical defect length in foveal ELM (μm)	0.532	< 0.001
Vertical defect length in foveal IS/OS (μm)	0.543	< 0.001

ELM external limiting membrane, *IS/OS* junction between inner and outer segments of the photoreceptors.

Table 4 Association of Final Visual Acuity with Measurement Values Obtained at Initial Examination

	Single regression analysis		Multiple regression analysis	
			Partial regression	
	regression coefficient	<i>P</i> -value	coefficient	<i>P</i> -value
Age (years)	0.365	0.017	0.232	0.090
Durations of symptom until initial examination (weeks)	-0.139	0.381	-	-
Visual acuity (logMAR)	0.329	0.033	0.154	0.233
Foveal thickness (μm)	0.496	< 0.001	0.374	0.006
Foveal cystoid spaces	0.290	0.063	-	-
Hemorrhage within foveal cystoid spaces	0.459	0.002	0.160	0.302
Foveal SRD	0.164	0.298	-	-
Foveal SRH	0.361	0.019	0.279	0.061
Status of foveal ELM	0.219	0.163	-	-
Status of foveal IS/OS	0.258	0.100	-	-
Retinal perfusion status	0.186	0.245	-	-

logMAR logarithm of the minimum angle of resolution, *SRD* serous retinal detachment, *SRH* subretinal hemorrhage, *ELM* external limiting membrane, *IS/OS* junction between inner and outer segments of the photoreceptors.

Table 5 Comparisons of Initial Visual Acuity and Final Measurement Values between Two Groups Classified by Initial Detection of Foveal

Subretinal Hemorrhage

	Initial subretinal hemorrhage		Initial subretinal hemorrhage		
	(-)		(+)		
	(24 eyes)		(18 eyes)		
	Mean ± SD	range	Mean ± SD	range	<i>P</i> -value
Initial visual acuity (logMAR)	0.41 ± 0.37	<u>0--1.05</u>	0.49 ± 0.32	<u>0.05--1.22</u>	0.490
Final visual acuity (logMAR)	0.14 ± 0.27	<u>-0.18--0.30</u>	0.37 ± 0.35	<u>-0.08--1.10</u>	0.019
Final foveal thickness (μm)	342.3 ± 105.0	<u>225--628</u>	399.5 ± 172.5	<u>227--791</u>	0.218
Vertical defect length in foveal ELM (μm)	88.6 ± 149.3	<u>0--550</u>	194.4 ± 233.1	<u>0--810</u>	0.085
<u>Horizontal defect length in foveal ELM (μm)</u>	87.0 ± 197.0	<u>0--800</u>	301.1 ± 337.2	<u>0--1000</u>	0.017
Vertical defect length in foveal IS/OS (μm)	163.3 ± 286.1	<u>0--1000</u>	436.3 ± 282.8	<u>0--1000</u>	0.004
<u>Horizontal defect length in foveal IS/OS (μm)</u>	88.6 ± 149.3	<u>0--800</u>	194.4 ± 233.1	<u>0--1000</u>	0.028

logMAR logarithm of the minimum angle of resolution, *ELM* external limiting membrane, *IS/OS* junction between inner and outer segments of the photoreceptors.

Figure 1
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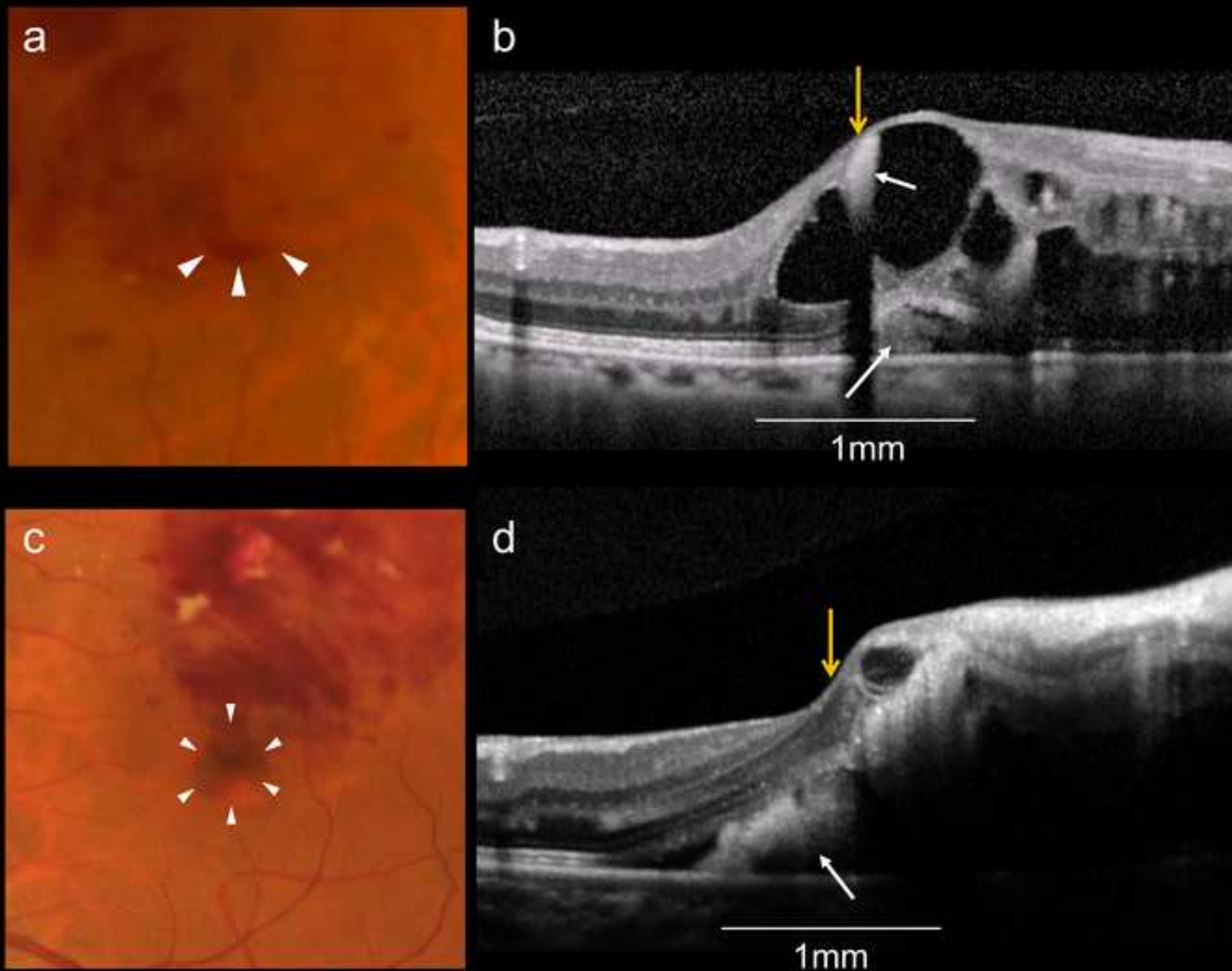


Figure 2
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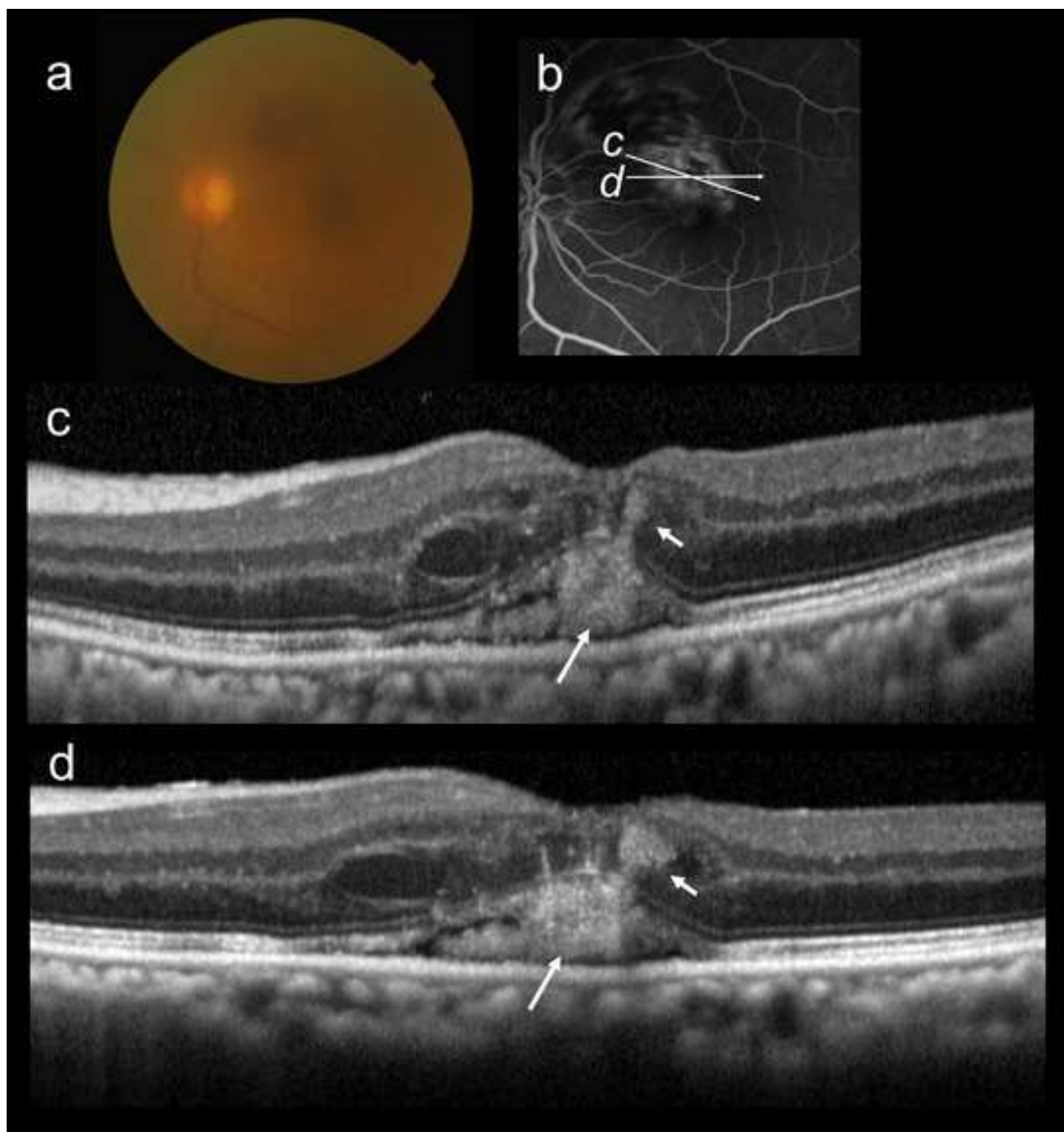


Figure 3
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