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DETECTION AND CHARACTERISTICS OF UNRUPTURED RETINAL ARTERIAL MACROANEURYSMS

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Purpose: To determine the presence of unruptured retinal arterial macroaneurysms (RAMs) and to examine the characteristics of the detected lesions.

Methods: This retrospective observational study included the affected and contralateral eyes of 50 patients (100 eyes) with symptomatic, unilateral, ruptured RAMs who visited the Department of Ophthalmology at the Kyoto University Hospital (April 2014–April 2020) and were followed up for at least 6 months after the onset. The presence and characteristics of unruptured RAMs were examined by reviewing the findings of color fundus photography and infrared scanning laser ophthalmoscopy performed before the onset or during the follow-up period.

Results: Unruptured RAMs were detected in six of the 50 patients. Some patients had bilateral or multiple unruptured RAMs, and a total of 12 unruptured RAMs were detected in eight eyes of the six patients. Among the detected lesions, eight exhibited a longitudinal increase in their diameter during the follow-up period, whereas six exhibited ruptures.

Conclusion: Unruptured RAM is not an uncommon retinal vascular abnormality and can enlarge and progress to ruptured RAM.

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Retinal arterial macroaneurysm (RAM) is an acquired dilation of a retinal artery, typically within the first three bifurcations of the central retinal artery.[1] Older age, female sex, and arteriosclerosis[2] are risk factors for RAM rupture. Most patients with ruptured RAMs have unilateral, solitary lesions, and approximately 10% show bilateral or multiple lesions.[2,3]

Several studies have reported pathological conditions[4] and treatment strategies[5–9] for eyes with ruptured RAMs, and this has improved our understanding regarding the condition. However, little is known about the presence of a subclinical precursor condition or the manner in which it progresses to RAM rupture; this is because RAM is generally diagnosed when patients experience a sudden decrease in their central vision after RAM rupture.

Accordingly, in the present study, we retrospectively reviewed the color fundus photographs and infrared scanning laser ophthalmoscopy images of patients with ruptured RAMs to determine the presence of unruptured RAMs and examine the characteristics of the detected lesions.

Methods

This retrospective observational study was approved by the Institutional Review Board of the Kyoto University Graduate School of Medicine (Kyoto, Japan) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was waived because of the retrospective nature of the study. Instead, a web page was created with information regarding the purpose of the study, where it was emphasized that any subject could opt out of the study at any time via telephone, fax, or e-mail notification.

We included patients with symptomatic, unilateral, ruptured RAMs who visited our department between April 2014 and April 2020 and were followed up for at least 6 months after the onset. Ruptured RAMs were diagnosed using fundus ophthalmoscopy, color fundus photography (TRC-50LX, Topcon, Tokyo, Japan; 3,216 × 2,136 pixels), fluorescein angiography (FA; occasionally with indocyanine green angiography [ICGA]; Spectralis HRA + OCT, Heidelberg Engineering, Heidelberg, Germany), and optical coherence tomography (OCT) (Spectralis HRA + OCT, Heidelberg

Engineering). Specifically, the diagnosis was based on hyperfluorescence of the affected retinal arteries on FA (and ICGA) and the corresponding intraretinal aneurysm on OCT. Linearity without undulation of the retinal pigment epithelial line on OCT images facilitated differentiation of polypoidal choroidal vasculopathy, which can show a hemorrhagic appearance similar to that of ruptured RAMs. In addition, sub–inner limiting membrane hemorrhage on OCT images is a highly specific finding for ruptured RAMs,[10] and it was useful for diagnosis. In this study, we considered RAMs other than unruptured RAMs (described below) as ruptured RAMs, which were almost synonymous with the hemorrhagic and exudative RAMs described in previous studies.[11,12]

We excluded patients with RAM accompanying uveitis, retinal vein occlusion, diabetic retinopathy, retinal vasculitis, and age-related macular degeneration. Eventually, 100 eyes (diseased eyes and contralateral eyes) of 50 consecutive patients met the inclusion criteria.

For examination of unruptured RAMs, we reviewed the color fundus photographs and infrared (IR) scanning laser ophthalmoscopy (SLO) images (Spectralis HRA + OCT, Heidelberg Engineering) acquired during the observation period. We slightly expanded the definition of quiescent RAM as previously described[11,12] and defined unruptured RAMs as RAMs without any retinal hemorrhage, edema, or hard exudates. We then examined whether unruptured RAMs could be detected. If lesions were detected, we determined whether their location was on the nasal or temporal side of the fovea and identified the ordinal number of branch from central retinal artery. Using the measurement software incorporated into the IR SLO device, we measured the distance between RAM and the fovea on the IR SLO images. Then, we calculated the average diameter from the vertical and horizontal diameters. In addition, for patients who had visited our department for any reason before the onset of RAM rupture, we examined the medical records obtained before the onset.

Results

There were 10 men and 40 women with a mean age of 78.9 ± 7.6 years. Six of the 50 patients had medical records prepared for some reason other than the exclusion criteria before RAM rupture.

Table 1 shows the clinical and ophthalmological characteristics of patients with unruptured RAMs and the locations of RAMs (Table 1). Six of the 50 patients (12%, one man and five women) had unruptured RAMs (Table 1); in total, 12 unruptured RAMs were detected in eight eyes of these six patients during the mean observation period of 26.8 ± 21.0 months. Table 2 shows the longitudinal changes in the unruptured RAMs. During the observation period, eight of the 12 unruptured RAMs (in six eyes of five patients) showed longitudinal enlargement, whereas the six unruptured RAMs (in six eyes of five patients) subsequently ruptured (Tables 1 and 2, Figure 1). The mean size of the unruptured RAMs was 111 ± 21 μm at the time of first detection and 140 ± 46 μm at the visit just before the rupture.

Discussion

In the present study including 100 eyes of 50 patients with acute RAM rupture, 12 unruptured RAMs were detected in eight eyes of six patients. Among the 12 unruptured RAMs, eight exhibited a longitudinal increase in their diameter, whereas six exhibited rupture (Table 1 and Figure 1).

Retinal arterial macroaneurysms is a clinically important retinal vascular disease, particularly in the

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None of the authors have conflicting interests to disclose.

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Table 1. General and Ophthalmological Characteristics of Patients With Unruptured and Ruptured RAMs

Case	Age (year), Sex	Systemic Disease	Others	Records Before Onset	Unruptured RAM (n)	Eyes with Unruptured RAM	Location of RAM	Ordinal Number of Branch from CRA	Distance from the Fovea (μm)	Initial VA	Period from Initial Visit to Detection (month)	Period from Detection to Rupture (month)	Final VA
1	71, M	HT	CS	None	3	Diseased	N	1	2,827	20/2000	3.4	NA	20/32
							N	2	2,410		3.4	NA	
						Contralateral	N	3	2,912	20/25	9.8	57	20/32
2	84, F	HT		None	4	Diseased	T	3	2,157	20/200	17.3	108	20/50
						Contralateral	T	3	1719	20/20	0	53	20/100
							T	3	1779		0	NA	
							T	3	1933		0	NA	
3	82, F			None	1	Contralateral	T	2	1,569	20/32	0	40	20/400
4	79, F	dysL		None	1	Contralateral	T	3	3,510	20/25	0	11	20/63
5	79, F	HT		None	2	Diseased	N	2	2,777	20/63	9.8	NA	20/63
							T	2	2,284		21.7	NA	
6	74, F	HT		Presence	1	Diseased	N	1	2,746	20/16	0	7	20/25
											Follow-up period		
7	77, M		CS	None	0		N	2	1,273	20/200	15		20/200
8	69, F	HT		None	0	N.A.	N	2	2,939	20/40	27	NA	20/40
9	71, F	HT, CD		None	0		T	3	2039	20/25	16		20/20
10	76, F	HT, DM		None	0		N	1	4,020	20/63	18		20/40
11	86, F	HT		None	0		N	1	4,728	20/40	6		20/40
12	83, F			None	0		N	2	2,914	20/400	14		20/50
13	82, M			None	0		T	3	2,183	20/32	41		20/200
14	89, M	HT	CS	None	0		N	2	2,690	20/25	23		20/20
15	69, F			None	0		T	2	3,504	20/20	54		20/16
16	66, F	HT, dysL		None	0		T	3	1,570	20/500	7		20/200
17	75, F			Presence	0		N	2	2,243	20/16	77		20/32
18	78, F			None	0		N	2	2,936	20/50	73		20/200
19	82, F	HT		None	0		T	2	3,211	20/40	8		20/32
20	81, F			None	0		T	2	2,344	20/100	61		20/40
21	81, F	HT, dysL		None	0		N	2	2,316	20/200	10		20/200
22	73, F	HT		None	0		N	2	2,225	20/400	67		20/25
23	73, F	HT		None	0	N.A.	N	2	4,849	20/400	62	NA	20/25
24	75, F			None	0		N	2	3,049	20/32	21		20/25
25	92, F			None	0		T	2	2,544	20/2000	13		20/200
26	83, M	HT	CS	None	0		T	3	2,747	20/25	11		20/25
27	72, M	HT	CS	None	0		T	2	2,617	20/16	7		20/32
28	78, F			None	0		N	1	2,137	20/500	21		20/200
29	86, F	HT		None	0		T	2	2,593	20/200	10		20/20
30	95, F	HT		None	0		N	2	4,259	20/40	25		20/25
31	78, M	HT	CS	None	0		N	2	1736	20/32	7		20/20
32	74, F	HT		None	0		T	3	2,171	20/200	30		20/200
33	75, F	HT		None	0		T	3	1,412	20/2000	10		20/200
34	53, F	HT, CD	ST/CS	None	0		T	3	1800	20/100	30		20/63
35	79, F	HT		None	0		N	2	3,333	20/63	40		20/40
36	86, F	HT		None	0		N	2	3,849	20/400	10		20/32
37	67, M	HT, dysL		None	0		N	2	1982	20/32	11		20/20

(*continued on next page*)

Table 1. (Continued)

Case	Age (year), Sex	Systemic Disease	Others	Records Before Onset	Unruptured RAM (n)	Eyes with Unruptured RAM	Location of RAM	Ordinal Number of Branch from CRA	Distance from the Fovea (μm)	Initial VA	Period from Initial Visit to Detection (month)	Period from Detection to Rupture (month)	Final VA
38	86, F	HT		None	0		N	3	774	20/200	27		20/100
39	87, F	HT	CS	None	0		N	2	4,199	20/250	35		20/200
40	89, M	HT		None	0		T	2	2072	20/63	15		20/100
41	90, F	HT		Presence	0		N	2	1,601	20/25	28		20/25
42	88, F	HT	CS	None	0		N	3	2,773	20/1,000	10		20/200
43	83, F	HT		None	0		N	3	4,674	20/250	24		20/16
44	82, F	HT, dysL	CS	None	0		N	2	2,316	20/16	6		20/32
45	76, F	HT, CD	ST	Presence	0		T	2	2,549	20/16	13		20/50
46	77, F	HT		None	0		T	3	2,784	20/16	19		20/16
47	80, F	HT		Presence	0	N.A.	N	3	4,435	20/16	56	N.A.	20/25
48	84, M	HT		None	0		N	2	2,455	20/32	6		20/32
49	73, F			Presence	0		N	3	3,638	20/16	17		20/20
50	75, F	HT		None	0		N	3	2,511	20/200	12		20/25

M, male; F, female; HT, systemic hypertension; dysL, dyslipidemia; CD, collagen disease; DM, diabetes mellitus; ST, steroid administration; CS, current smoker; CRA, central retinal artery; RAM, retinal arterial microaneurysm; n, number; T, temporal side of the fovea; N, nasal side of the fovea; VA, visual acuity; NA, not applicable.
The initial and final VAs are shown as Snellen VA ratios.

elderly. It can cause massive hemorrhage, leading to sudden visual impairment in the affected eye. Although the visual prognosis has slightly improved following advances in the management and the development of treatment strategies, such as subretinal injection of tissue plasminogen activator,[8,13] the visual outcome remains limited in patients with severe, irreversible damage in the macula. With regard to ruptured RAMs, associations of the visual prognosis with the fluffy sign[14] and three-dimensional intraretinal positions of RAM[15] were recently reported, improving our understanding of the abnormalities. However, there is little information regarding the existence of unruptured RAMs or their progression to ruptured RAMs.

In 1987, Lavin et al[11] found quiescent RAMs in 10 (10 eyes) of 40 patients with RAM. The authors defined quiescent RAMs as RAMs with surrounding retinal hemorrhage or exudates within an area of less than 1 disk diameter, without involvement of the macula.[11]However, the image quality in their study was not adequate, and six patients (75%) had comorbid retinal vein occlusion and diabetic retinopathy.[11] In 2006, Moosavi et al[12] examined FA findings in 40 cases of RAM. In their report, quiescent RAMs were defined as RAMs without hemorrhage or exudate or RAMs with existing retinal hemorrhage and/or exudate without the involvement of the macula or loss of visual acuity.[12] However, 13 of the 14 cases classified as quiescent RAM were reported to have retinal hemorrhage or other exudative changes.[12] This indicates that reports regarding RAM without any hemorrhage or exudative changes are scarce. Accordingly, we defined unruptured RAMs in the present study as RAMs without any abnormality in the surrounding retinal parenchyma, and we considered RAMs other than unruptured RAMs as ruptured RAMs. Thus, the definition of unruptured RAM may not be completely validated, and we examined a more immature and subclinical condition than that (quiescent RAM) described in the previous studies.[11,12]

For the examination of unruptured RAMs, we used IR SLO images that were always acquired simultaneously with OCT images at each visit. However, SLO reportedly has higher resolution and contrast than does color fundus photography,[16] and it is useful for evaluating morphological changes in the retinal arterial wall and intra-aneurysmal hemodynamics.[17,18] Infrared SLO used in the present study facilitated identification of unruptured RAMs that were not surrounded by any retinal hemorrhage or other incidental lesions. In this study, 67% of the detected unruptured RAMs showed a longitudinal and gradual increase in size (Figure 1 and Table 2). Moreover, 50% progressed

Table 2. Detection of Unruptured RAMs and Longitudinal Changes in Detected Lesions

Case	Eyes with Unruptured RAM	Size of Unruptured RAM at the Time of Detection	Size of Unruptured RAM at Visit 1/Duration after Detection	Size of Unruptured RAM at Visit 2/Duration after Detection	Duration from Detection to Rupture of the Unruptured RAM
1	Diseased	114 μm	148 μm/6.4 months	152 μm/67 months	NA
	Diseased	90 μm	184 μm/6.4 months	197 μm/67 months	NA
	Contralateral	131 μm	NA	NA	57
2	Diseased	84 μm	129 μm/36 months	NA	108
	Contralateral	109 μm	NA	NA	53
	Contralateral	91 μm	100 μm/53 months	110 μm/125 months	NA
	Contralateral	94 μm	102 μm/53 months	104 μm/125 months	NA
3	Contralateral	98 μm	110 μm/9.7 months	NA	40
4	Contralateral	Unknown	NA	NA	11
5	Diseased	145 μm	148 μm/6.1 months	150 μm/12 months	NA
	Diseased	131 μm	NA	NA	NA
6	Diseased	133 μm	221 μm/5.7 months	NA	6.9
				NA	

NA, not applicable.

to ruptured RAM (Tables 1 and 2). In unruptured cerebral aneurysms, increased cerebral blood flow or blood flow abnormalities such as turbulence could exacerbate macrophage-mediated inflammation, resulting in remodeling of the vessel wall.[19] In RAMs, narrowing of the retinal artery as a result of aging or systemic hypertension and the consequent blood flow alterations may contribute to the formation of unruptured RAMs. Most recently, it was reported that formation of splits in the vessel wall of retinal arteries might be involved in the development of ruptured RAM.[20] If the spilt is formed and enlarged during the process of expansion of an unruptured RAM, it might increase the possibility of RAM rupture.

Limitations

This study has some limitations. First, it was a retrospective observational study. Because we could not recognize most of the unruptured RAMs in real time, FA and OCT were not used for the identification of unruptured RAMs. Second, medical records before the onset were unavailable for most patients, and it was quite possible that the variations among patients affected the rate of detection of unruptured RAMs. Third, we could not precisely determine the incidence of unruptured RAMs or the risk of rupture, given the variations in the observation period and the limited number of participants.

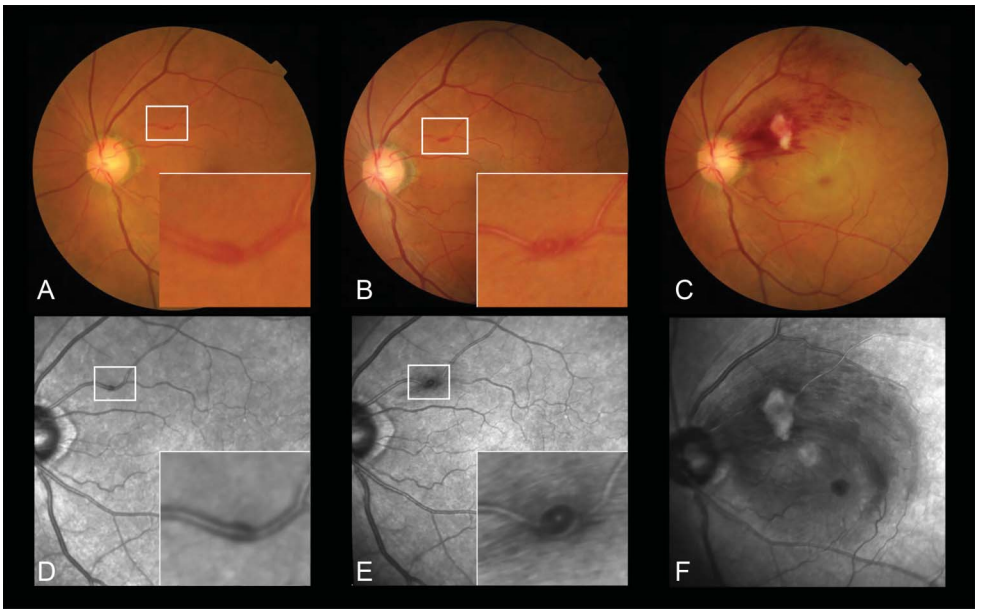

Fig. 1. A representative case involving a 74-year-old woman with an unruptured RAM. **A–C.** Color fundus photographs and (**D, F**) IR SLO images. **A, D.** Six months before RAM rupture. The diameter of the unruptured RAM (length perpendicular to the course of the affected artery) was 133 μm on the IR image. **B, E.** One month before RAM rupture. The diameter was increased to 221 μm on the IR image. The Snellen visual acuity was 20/17. **C, F.** At the time of RAM rupture, the Snellen visual acuity decreased to 20/400.

Nevertheless, we were able to detect unruptured RAM, which has been a largely unknown condition thus far. In addition, we observed that some unruptured RAMs enlarged and progressed to ruptured RAMs. Prospective studies with larger numbers of participants are warranted to determine the prevalence of unruptured RAM and the risk for progression to ruptured RAM.

Key words: retinal arterial macroaneurysm, rupture, unruptured, unruptured retinal arterial macroaneurysm.

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