Online March 8, 2022
Journal of Neuroendovascular Therapy 2022; 16: 387–394 DOI: 10.5797/jnet.oa.2021-0089

Original Article

Characteristics of Unruptured Intracranial Aneurysms with Delayed Rupture Following Coil Embolization: Case Series and Review of the Literature

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Objective: Long-term clinical outcomes including delayed rupture of unruptured intracranial aneurysms (UIAs) after coil embolization (CE) remain unclear. The purpose of this study was to evaluate the precise timing of re-treatment for recanalized UIAs before rupture.

Methods: From February 2012 to June 2020, a total of 197 patients with 207 UIAs underwent CE in our institution and were followed up for more than 6 months. The follow-up period, as well as morphological changes from treatment to recanalization, regrowth, and rupture, was retrospectively analyzed. Delayed rupture was defined as a rupture that occurred more than 1 month after CE.

Results: The average length of follow-up was 48.7 months. Three of 207 UIAs (1.45%) ruptured after CE. The aneurysm locations were the middle cerebral artery (MCA), anterior communicating artery (AcomA), and internal carotid artery–posterior communicating artery (ICA–Pcomm). The annual rupture rate after CE was 0.36%. Immediately after the first CE, treated aneurysms were graded according to the Modified Raymond–Roy Classification with class II for MCA aneurysms and class IIIb for AcomA and ICA–Pcomm aneurysms. The ICA–Pcomm aneurysm was treated with two additional CEs and was finally graded as class I. In all cases, DSA or MRA before aneurysm rupture showed recanalization and regrowth of aneurysms. The average periods from final embolization to regrowth and from regrowth to rupture were 54.3 months (±16.8) and 2.3 months (±0.9), respectively.

Conclusion: UIAs with recanalization and regrowth after CE should undergo re-treatment as early as possible.

Keywords ▶ unruptured intracranial aneurysm, delayed rupture, coil embolization, recanalization, regrowth

Introduction

Delayed rupture after a long period of time following coil embolization (CE) for ruptured intracranial aneurysms (RIAs) has been reported in the International Subarachnoid Aneurysm Trial (ISAT) and the Barrow Ruptured Aneurysm Trial (BRAT).[1,2] Therefore, long-term follow-up is considered to be important for RIAs. On the other hand, the possibility of delayed rupture after CE for unruptured intracranial aneurysms (UIAs) remains unclear compared with that for RIAs, and the need for long-term follow-up and re-treatment for recanalization after CE for UIAs has not been clearly defined. Here, we present a case series of UIAs that ruptured after CE and analysis of their specific characteristics.

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Materials and Methods

Patient and aneurysm characteristics

From February 2012 to June 2020, a total of 197 patients with 207 UIAs underwent CE in our institute and were followed up for more than 6 months. Fusiform aneurysms, dissecting aneurysms, recurrent aneurysms previously treated with coiling, and aneurysms treated with parent artery occlusion were excluded from this analysis. Treatment of UIAs was performed after careful assessment of perceived risk factors for rupture based on clinical studies as previously described.[3–5)]

Patient characteristics including aneurismal location, morphological assessment of aneurysm such as aneurysm volume, aneurismal change after CE, and follow-up period until rupture were retrospectively analyzed. Delayed rupture was defined as a rupture that occurred more than 1 month after CE.

This study was conducted in accordance with the Declaration of Helsinki and with the approval of the ethics committee.

Antiplatelet therapy

When aneurysms were treated by CE without a stent, a single antiplatelet agent (100 mg aspirin) was administered daily for 1–2 weeks before the procedure and was discontinued for 1–4 weeks after the procedure. For aneurysms treated by CE with a stent, dual-antiplatelet agents (100 mg aspirin and 75 mg clopidogrel) were administered daily for 1–2 weeks before the procedure and maintained until 6 months postoperatively; then a single antiplatelet drug (100 mg aspirin) was continuously given for another 6 months.

Endovascular procedures

The best approach and technique for the endovascular procedure (i.e., simple technique, double-catheter technique, balloon-assisted CE, or stent-assisted CE) were performed by a neurovascular team. All surgical procedures were performed with the patient under general anesthesia.

Evaluation of coiled aneurisms

The Modified Raymond–Roy Classification (MRRC) and volume embolization ratio (VER) with NeuroVision (Cybernet Systems, Tokyo, Japan) were assessed to confirm the completeness or residual patency of the aneurysm immediately after treatment.[6,7)] All radiological findings were estimated by two board-certified neuroendovascular surgeons. In case of disagreement between reviewers, a third neuroendovascular surgeon reviewed the case, and consensus was reached.

Definition of recanalization and regrowth of aneurysms after CE; therapeutic implication for re-treatment

Recanalization was defined as an increased blood flow into the aneurysms compared with initial findings on DSA or MRA immediately after embolization. The degree of recanalization was divided into minor and major. The minimum coil compaction at the aneurysmal neck was classified as minor recanalization. Contrast filling within the aneurysmal sac and marked coil loosening, including coil compaction and extruding of the coil mass beyond the original aneurysmal boundary, were classified as major recanalization.[8)]

Regrowth was defined as ≥1.2-fold increase in the diameter of the coiled aneurysm or the appearance of a de novo bleb.

In general, follow-up DSA was scheduled for 1 year after CE. Aneurysms with or without minor recanalization[8)] were conservatively observed by MRA every 6–12 months after the follow-up DSA.

When major recanalization[8)] or regrowth of aneurysm was identified by follow-up DSA or MRA, additional treatment was strongly recommended to patients and informed consent was obtained.

Results

A total of 207 UIAs were treated by CE, and the average length of follow-up was 48.7 months after treatment. The characteristics of 207 UIAs are shown in **Table 1**. Recanalization and regrowth were identified in 50 (24.2%) and 15 (7.2%) aneurysms, respectively (**Fig. 1**). Re-treatment before rupture was performed in 17 (8.2%) aneurysms by additional CE instead of clipping or parent artery occlusion. One of the 17 aneurysms ruptured regardless of re-treatment as described in the following (**Fig. 1**, Case 3). Three aneurysms ruptured after CE (1.45% of total coil-embolized aneurysms), and the annual rupture rate was 0.36% (**Fig. 1** and **Table 2**). The location of the three aneurysms was the anterior communicating artery (AcomA), the internal carotid artery–posterior communicating artery (ICA-Pcomm), and the middle cerebral artery (MCA). The average maximum size of the aneurysms was 7.1 mm (±0.6). Immediately after the initial CE, embolized aneurysms were graded as class II for MCA aneurysms and class IIIb for AcomA and ICA–Pcomm aneurysms, according to the MRRC. The ICA–Pcomm aneurysm defined as

Table 1 Characteristics of 207 UIAs

Characteristics	UIAs (n = 207)
Age, years	
Mean (SD)	64.8 (11.5)
Sex, n (%)	
Female	141 (68.1)
Aneurysm location, n (%)	
ICA, except Pcomm	54 (26.1)
ICA–Pcomm	40 (19.3)
MCA	36 (17.4)
AcomA	36 (17.4)
ACA	11 (5.3)
VA	9 (4.3)
BA	19 (9.2)
Others	2 (1.0)
Maximum aneurysm diameter, mm	
Mean (SD)	6.6 (2.3)
Distribution, n (%)	
<5 mm	52 (25.1)
5–9 mm	135 (65.2)
≥10 mm	20 (9.7)
Mean aneurysm neck size, mm (SD)	5.0 (1.9)
Endovascular procedure, n (%)	
Simple	94 (45.4)
Balloon assisted	34 (16.4)
Double catheter	57 (27.5)
Stent assisted	22 (10.6)
Without stent	185 (89.4)
MRRC, n (%)	
Class I	64 (30.9)
Class II	108 (52.2)
Class IIIa	7 (3.4)
Class IIIb	28 (13.5)
VER, %	
Mean (SD)	24.2 (5.6)
Recanalization, n (%)	50 (24.2)
Regrowth, n (%)	15 (7.2)
Retreatment, n (%)	17 (8.2)
Rupture, n (%)	3 (1.45)
Follow-up period, month	
Mean (SD)	48.7 (30.0)

ACA: anterior cerebral artery; AcomA: anterior communicating artery; BA: basilar artery; ICA: internal carotid artery; ICA–Pcomm: bifurcation of the internal carotid artery and posterior communicating artery; MCA: middle cerebral artery; MRRC: Modified Raymond–Roy Classification; SD: standard deviation; UIAs: unruptured intracranial aneurysms; VA: vertebral artery; VER: volume embolization ratio

class IIIb after initial treatment subsequently underwent two additional treatments with CE and was finally graded as class I. In all cases, DSA or MRA prior to rupture revealed recanalization followed by regrowth of the aneurysms. The average durations from the final CE to regrowth and from regrowth to rupture were 54.3 months (±16.8) and 2.3 months (±0.9), respectively.

Case Presentations

Case 1

A 50-year-old woman presented with a mild headache, and she was diagnosed with a right MCA UIA with a maximum diameter of 7.7 mm on MRA (**Fig. 2A**). The aneurysm was embolized with a simple technique using 10 coils with a length of 50 cm. The result of CE was an MRRC class II aneurysm and a VER of 21.8% with Neurovision (**Fig. 2B**). Follow-up DSA 12 months after the initial CE showed that the aneurysm was recanalized to an MRRC class IIIb aneurysm (**Fig. 2C**).

Seventy-four months after the initial CE, MRA revealed de novo formation of the aneurysm (**Fig. 2D**). De novo formation of the dome was also evaluated with DSA (**Fig. 2E**). Although re-treatment was scheduled, 3 months after de novo formation was found on MRA, the aneurysm ruptured, resulting in World Federation of Neurological Surgeons (WFNS) grade 1 subarachnoid hemorrhage (SAH). Re-treatment was performed immediately after the aneurysm ruptured. CE resulted in an MRRC class II aneurysm (**Fig. 2F**). The postoperative clinical course was uneventful without re-rupture. The patient was discharged 21 days after the treatment with a modified Rankin Scale of 0. DSA 12 months after the second embolization showed a slight neck remnant, but no re-growth of the aneurysm was seen.

Case 2

A 52-year-old man with a history of polycystic kidney disease, hypertension, and dyslipidemia was incidentally diagnosed with an AcomA aneurysm on MRA (**Fig. 3A**). Because the size of the aneurysm was growing during follow-up, we considered treatment for the aneurysm. CE was performed with a simple technique using three coils with a length of 13 cm. The treatment resulted in an MRRC class IIIb aneurysm and a VER of 19.7% (**Fig. 3B** and **3C**).

Twelve months after the initial CE, no recanalization was found with DSA (**Fig. 3D**). MRA was performed every 6 months in an outpatient clinic. Twenty-eight months after the initial CE, recanalization was found on MRA. Regrowth of the aneurysm was detected 33 months later, and SAH occurred 34 months later (WFNS grade IV) (**Fig. 3E**). De novo bleb formation was found on DSA (**Fig. 3F** and **3G**). Immediately after the SAH, the aneurysm was treated with a simple technique with four coils with a length of 15 cm, and the treatment resulted in an MRRC class IIIb aneurysm without any complications (**Fig. 3H**).

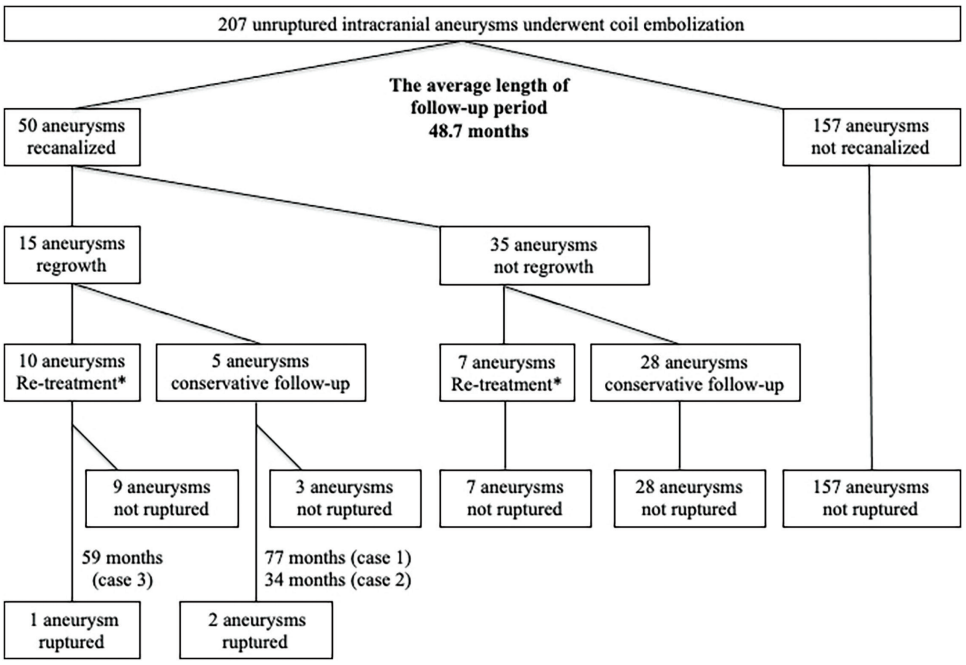

Fig. 1 Study flowchart. Recanalization and regrowth were identified in 50 (50/207; 24.2%) and 15 (15/207; 7.2%) aneurysms, respectively. *Re-treatment before rupture was performed in 17 (17/207; 8.2%) aneurysms by additional CE instead of clipping or parent artery occlusion. One of the 17 aneurysms (case 3) ruptured regardless of re-treatment. CE: coil embolization

Table 2 Characteristics of UIAs with delayed rupture after CE

Case	Authors, year	Age (years)/ sex	Site of the aneurysm	Maximum diameter (mm)	MRRC	VER (%)	Period (months)			Final mRS
							From embolization to recanalization	From recanalization to regrowth	From regrowth to rupture	
1	Onishi et al., 2015[14]	75/M	BA tip	7.9	IIIa	22.9	18	30	20	6
2	Present case	50/F	MCA	7.7	II	21.8	12	62	3	0
3	Present case	52/M	AcomA	6.3	IIIb	19.7	28	5	1	1
4	Present case	72/M	ICA–Pcomm	7.3	I*	15.4	12	44	3	6

*In Case 4, the aneurysm was defined as class IIIb after initial treatment; subsequently, the aneurysm underwent additional treatment twice by CE and was finally graded as class I.
AcomA: anterior communicating artery; BA: basilar artery; CE: coil embolization; F: female; ICA–Pcomm: bifurcation of the internal carotid artery and posterior communicating artery; M: male; MCA: middle cerebral artery; MRRC: Modified Raymond–Roy Classification; mRS: modified Rankin Scale; UIAs: unruptured intracranial aneurysms; VER: volume embolization ratio

The patient recovered without neurological deficits except for visual impairment due to Terson syndrome. The patient was discharged 50 days after the re-treatment. At 7 months after the second CE, additional embolization for the residual compartment of the aneurysm was performed using six coils with a length of 16 cm. Treatment resulted in an MRRC class II aneurysm. MRA performed 60 months after the third embolization demonstrated no recanalization.

Case 3

A 72-year-old man had a history of Parkinson's disease, dyslipidemia, and vertigo. A right ICA–Pcomm aneurysm with a maximum diameter of 7.3 mm was incidentally found with MRA (**Fig. 4A**). The aneurysm was embolized with a balloon-neck remodeling technique using nine coils with a length of 54 cm. CE resulted in an MRRC class IIIb aneurysm and a VER of 15.4% (**Fig. 4B**). Because the

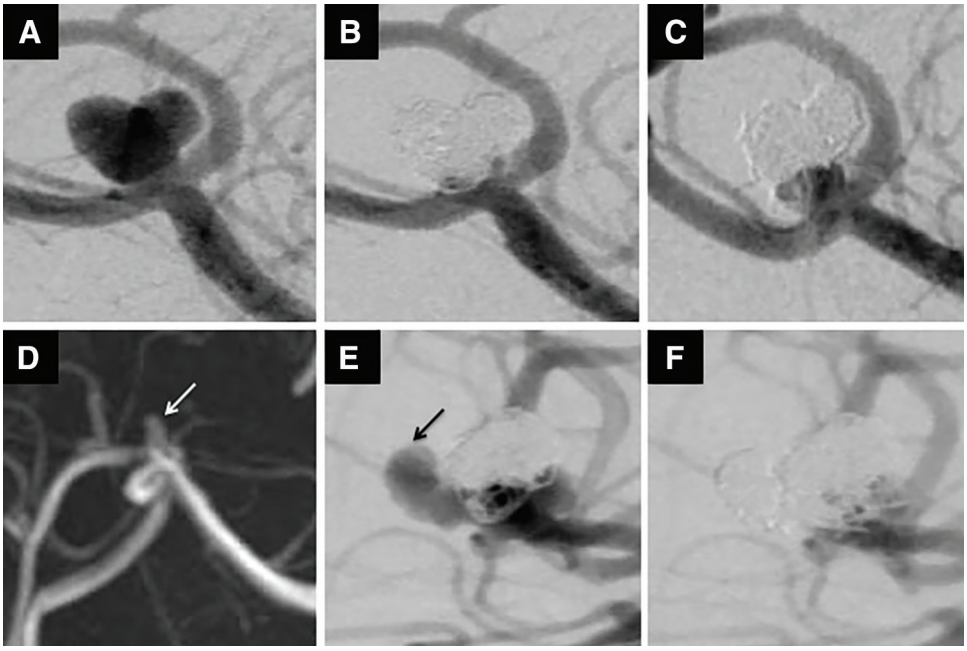

Fig. 2 Initial DSA showing an unruptured middle cerebral aneurysm (**A**). DSA immediately after (**B**) and 12 months after (**C**) embolization. The coil and the MRRC class II occlusion and MRRC class IIIb recanalization, respectively, are seen. MRA (**D**) and DSA (**E**) 74 months after embolization, demonstrating aneurysm growth (white arrow) and progression of recanalization with a de novo bleb (black arrow), respectively. DSA immediately after re-treatment for a ruptured aneurysm showing MRRC class II occlusion (**F**). MRRC: Modified Raymond–Roy Classification

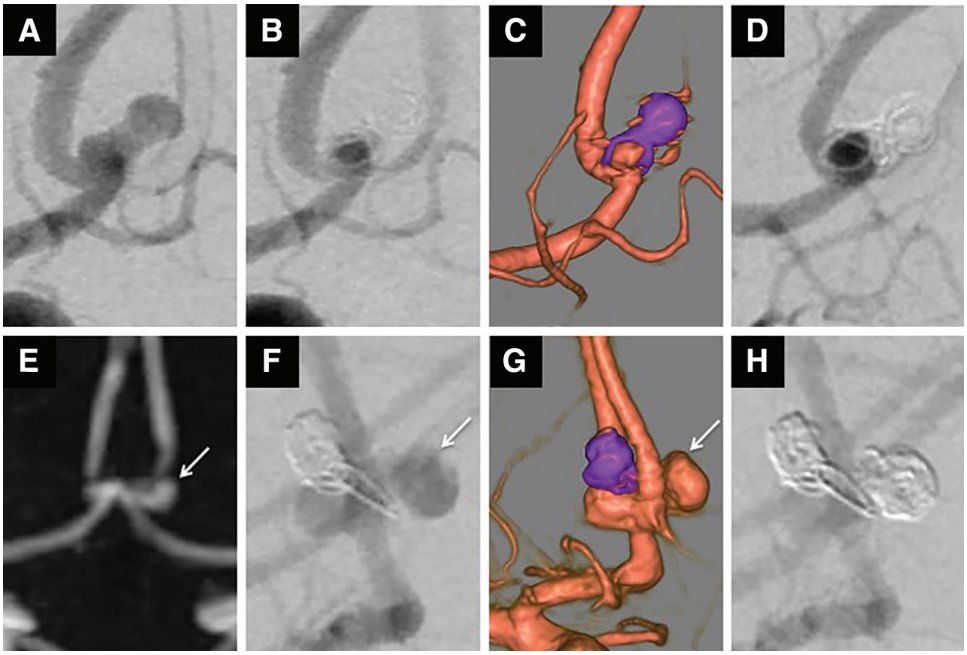

Fig. 3 Initial DSA showing an unruptured AcomA aneurysm (**A**). DSA (**B**) and 3D-DSA (**C**) immediately after embolization showed MRRC class IIIb occlusion. DSA 12 months after embolization showed no recanalization (**D**). MRA 33 months (**E**) after embolization demonstrating recanalization of the aneurysm and growth (white arrow). When the aneurysm ruptured, DSA (**F**) and 3D-DSA (**G**) demonstrated recanalization with a new bleb (white arrows). DSA immediately after re-treatment showing MRRC class IIIb occlusion (**H**). AcomA: anterior communicating artery; MRRC: Modified Raymond–Roy Classification

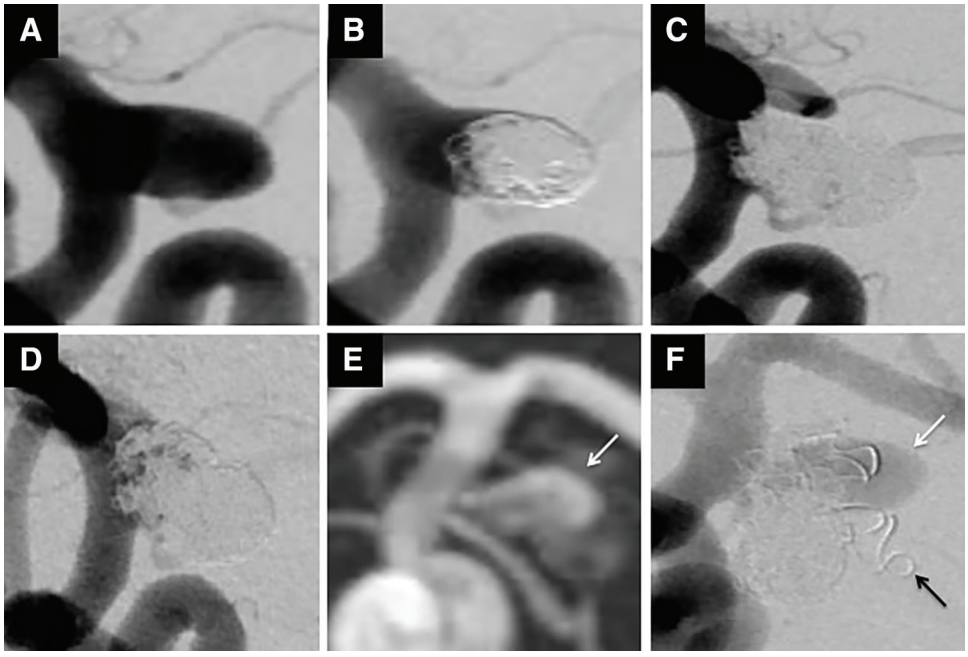

Fig. 4 Initial DSA showing an unruptured posterior communicating artery aneurysm (**A**). DSA immediately after the first (**B**) and third (**C**) CE showing MRRC class IIIb and class I occlusion, respectively. DSA 12 months after the third embolization demonstrating MRRC class IIIa recanalization (**D**). Both MRA (**E**) and DSA (**F**) 56 months after the third embolization demonstrated that the size of the recanalized aneurysm was enlarged (white arrow) and the coils (black arrow) were dispersed. MRRC: Modified Raymond–Roy Classification

aneurysm became recanalized repeatedly after CE, two additional CEs were performed. For the third session, CE was performed with a stent-assisted technique and resulted in an MRRC class I aneurysm (**Fig. 4C**).

One year after the third session, DSA showed mild recanalization that was graded as an MRRC class IIIa aneurysm (**Fig. 4D**). MRA 56 months after the third CE demonstrated that the aneurysm was growing (**Fig. 4E**). Subsequent DSA revealed that the coils had collapsed, and de novo formation was found (**Fig. 4F**). Although re-treatment was scheduled, the aneurysm ruptured. The patient died 59 months after the third treatment.

Discussion

The present cases suggested that UIAs after CE can become recanalized and occasionally regrow, even after a long period of stability. Once the aneurysm enlarged, it was occasionally accompanied with a de novo bleb, which were more likely to rupture during a short period of time.

Long-term follow-up after CE for RIAs is usually necessary. Regarding delayed rupture during a long period of time after CE for RIAs, the ISAT reported that the annual risk of re-rupture of coiled aneurysms was 0.156% in a period of 1–17.6 years,[1] and the BRAT showed that two of 83 coiled aneurysms re-ruptured at 7.5 and 9.5 years after treatment in a period of 10 years.[2] Therefore, long-term follow-up is considered to be important for surveying RIAs. On the other hand, according to previous reports, long-term clinical outcomes including delayed rupture after CE for UIAs are extremely rare compared with RIAs. The annual rupture rate after CE for UIA was 0.09%–0.2%.[9,10] In our study, a total of 197 patients with 207 UIAs were observed for an average length of 48.7 months. Among them, only three UIAs ruptured after CE, and the annual rupture rate was 0.36%. As described earlier, careful long-term follow-up should be required after CE for UIAs as well as for RIAs, because UIAs that were identified as regrowth following recanalization might rupture for a short period of time.

A previous report suggested that the risk of delayed rupture in UIAs after CE tended to increase in aneurysms with dome filling, symptomatic aneurysms, and large/giant aneurysms.[11] Computational fluid dynamic analysis has shown that recanalization may be affected by hemodynamic force[12] and that the rupture point is likely to be located where the blood flow impinges.[13] Furthermore, blood along the wall of an MRRC class IIIb aneurysm may promote coil compaction and/or lead to increased wall stress, causing aneurysm growth.[6] MRRC class IIIb aneurysms, which

could be exacerbated by blood flow against the aneurysm wall, tended to rupture frequently compared with class II and IIIa aneurysms after CE.[10] Based on serial images of complete occlusion, residual neck, dome filling, and rupture, Onishi et al. suggested that re-treatment should be performed when dome filling reaches the tip of an aneurysm or the aneurysm shows growth.[14] In the present study, in case 1, an MRRC class II aneurysm developed into an MRRC class IIIb aneurysm 12 months after embolization due to coil compaction. In case 2, DSA immediately after the CE showed an MRRC class IIIb aneurysm. In the two cases, subsequent serial radiological images revealed that an increased blood flow into the residual wall of the aneurysm might have induced de novo bleb formation as described earlier.[6,10] On the other hand, in case 3, the MRRC class I aneurysm developed into an MRRC class IIIa aneurysm 12 months after the third embolization. In this case, the recanalized segment that reached to the tip of the aneurysm dome might have developed regrowth and rupture of the aneurysm as Onishi et al. described.[14] The present cases suggested that not only MRRC class IIIb but also MRRC class IIIa aneurysms with progressive coil compaction could develop de novo bleb formation.

Early re-treatment is essential when regrowth is observed after CE of UIA. Among 30 cases of delayed rupture of UIAs after CE reported in previous literature since 2000,[9–11,14–29] there was only one report that represented precisely the period from recanalization to regrowth and from regrowth to rupture by reviewing serial neuroimages prior to rupture (**Table 2**).[14] In this report, the time from recanalization to regrowth and from regrowth to rupture was 30 months and 20 months, respectively. On the other hand, in our cases, the average period from recanalization to regrowth and from regrowth to rupture was 37.0 months and 2.3 months, respectively. The reason why the period from regrowth to rupture was extremely shorter in our series than in Onishi et al.'s case[14] might attribute to morphological differences at the time of regrowth. The aneurysm was "diffusely" enlarged in Onishi et al.'s case. In contrast, all our series of delayed rupture aneurysms were "locally" enlarged. Thus, when local regrowth of the recanalized aneurysm with a new bleb is observed after CE, it is more likely to rupture in a shorter period than previously reported. In addition, three delayed ruptured aneurysms revealed local regrowth pattern compared with three aneurysms that remained unruptured during conservative follow-up (**Fig. 1**, angiographical data not shown). Based on these findings and previous literature,[10,14,30] re-treatment for aneurysms with local regrowth pattern associated with the appearance of a de novo bleb should be performed as early as possible.

Limitation

The first limitation of the present study was the paucity of the number in our cohort due to rarity of rupture of UIAs following CE. Thus, statistical analyses could not be performed.

Second, five regrown aneurysms with conservative follow-up included three aneurysms (60%) unruptured and two aneurysms (40%) ruptured (**Fig. 1**). Thus, it is controversial whether all regrown aneurysms after CE should undergo early re-treatment. Although local regrowth is more likely to rupture in a shorter period as described earlier, we could not determine whether regrown aneurysms are classified as local. To address this issue, further studies on the relationship between regrowth pattern and latent period until rupture of UIA after CE will be needed.

Third, assessment of aneurismal regrowth in the present study is dependent on subjective judgment by board-certified neuroendovascular surgeons. Coil artifact made it difficult to measure volume of the coiled aneurysm including coil and enlarged components, regardless of assessment by 3D-DSA.[30] To conquer this problem, objective modalities will be needed.

Conclusion

After CE for UIAs, long-term follow-up is important. UIAs with recanalization and regrowth after CE should undergo re-treatment as early as possible.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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