Case Report

Repeated *de novo* aneurysm formation after anastomotic surgery: Potential risk of genetic variant *RNF213* c.14576G>A

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Abstract

Background: *De novo* aneurysm formation after intracranial anastomotic surgery is a relatively rare complication with fewer than 20 reported cases, and the mechanism is still unclear.

Case Description: A 63-year-old male treated for symptomatic internal carotid artery occlusion developed *de novo* aneurysms twice after anastomoses first of the superficial temporal artery-middle cerebral artery and second of the external carotid artery-radial artery-middle cerebral artery over a 10-year period. The first *de novo* aneurysm was successfully resected with pathological diagnosis of true aneurysm. The second *de novo* aneurysm thrombosed naturally after gradual growth. Genetic testing of the patient revealed the c.14576G>A (p.R4859K) variant in *ring finger protein 213*, which is a susceptibility gene for moyamoya disease.

Conclusions: This genetic variant was probably involved in the repeated *de novo* aneurysm formation, and this case represents a rare phenotype of the genetic variant.

Key Words: *de novo* aneurysm, external carotid artery-internal carotid artery anastomosis, internal carotid artery occlusion, moyamoya disease, *RNF213*

INTRODUCTION

External carotid artery (ECA)-internal carotid artery (ICA) anastomosis is a well-established surgical procedure for the treatment of ischemic cerebrovascular disease such as moyamoya disease (MMD), and giant cerebral aneurysms combined with major artery ligation.[1,2,8] *De novo* aneurysm formation after intracranial anastomotic surgery is relatively rare but life-threatening, with fewer than 20

reported cases [Table 1].[1,3,4,7,9–13,20–23,25] The mechanism of *de novo* aneurysm formation after anastomotic surgery may involve mechanical arterial wall injuries caused by intraoperative manipulations,[13] disproportion between donor and recipient vessels,[12] and insufficiency of sutures.[24] In contrast, some cases with long intervals of more than 20 years from anastomotic surgery to aneurysm formation may involve hemodynamic stress due to the increased hemodynamic force from the donor artery.[7,11,21]

Table 1: Series of *de novo* aneurysms after intracranial anastomotic surgery

Author and Year	Sex	Primary Diagnosis	Age at primary diagnosis	Anastomosis	Interval	Onset	Aneurysm site	Treatment	Pathology	Outcome
Fleischer *et al.*, 1979	M	ICA occlusion	60	STA-MCA	30 days	TIA	Anastomosis (M4)	Naturally thrombosed, OA-MCA	Pseudo	GR
Leclercq and Ambler, 1980	M	ICA occlusion	61	STA-MCA	25 days	Ruptured	Anastomosis (M4)	None	Pseudo	D
Parent and Smith, 1981	M	ICA occlusion	60	STA-MCA	41 days	Incidental	Anastomosis (M4)	Clipping	True	GR
Lantos *et al.*, 1984	M	ICA occlusion	70	STA-MCA	2 months	Incidental	Anastomosis (M4)	Coating	True	GR
Morgan *et al.*, 1986	M	BA stenosis	60	STA-SCA	11 months	Ruptured	Anastomosis (BA)	Ligation, contralateral STA-SCA	Pseudo	MD
Kohno *et al.*, 1996	F	ICA occlusion	65	STA-MCA	2.5 months	Ruptured	Anastomosis (M4)	Trapping, OA-MCA	True	GR
Sasaki *et al.*, 1996	M	MCA occlusion	49	STA-MCA	4 years	Ruptured	Anastomosis (M4)	Clipping	True	MD
Nishizawa *et al.*, 2000	M	ICA occlusion	43	STA-MCA	5 years	Ruptured	Anastomosis (M4)	Clipping	Pseudo	MD
Nishimoto *et al.*, 2005	M	MMD	31	STA-MCA	20 years	Ruptured	Anastomosis (M4)	Clipping	True	SD
Kurokawa *et al.*, 2007	F	ICA aneurysm	53	STA-MCA	3 years	Incidental	Anastomosis (M4)	None	True	GR
	M	ICA occlusion	49	STA-MCA	21 years	Incidental	Anastomosis (M4)	None	True	D
Hokari *et al.*, 2010	F	MCA occlusion	50	STA-MCA	27 years	Ruptured	Anastomosis (M4)	Trapping	Pseudo	D
Eom *et al.*, 2010	F	MMD	51	STA-MCA	6 months	Ruptured	Anastomosis (M4)	Aneurysm resection	Ttrue	SD
Aoki *et al.*, 2012	F	ICA aneurysm	43	STA-MCA	14 years	Ruptured	Remote (M2-M3)	Clipping	True	MD
Kawahara *et al.*, 2013	M	ICA occlusion	77	STA-MCA	2 years	Ruptured	Anastomosis (M4)	Clipping	Pseudo	SD
Present case	M	ICA occlusion	63							
1st aneurysm				STA-MCA	2.5 years	Incidental	Anastomosis (M4)	Trapping, ECA-RA-MCA	True	GR
2nd aneurysm				ECA-RA-MCA	4 years	Incidental	Remote (M3)	Naturally thrombosed	True	GR

BA: Basilar artery, D: Dead, F: Female, GR: Good recovery, M: Male, MD: Moderate disability, OA: Occipital artery, SCA: Superior cerebellar artery, SD: Severe disability, TIA: Transient ischemic attack

We describe an extremely rare case of repeated *de novo* aneurysm formation after first and second ECA-ICA anastomoses for symptomatic ICA occlusion. Genetic analysis of the patient revealed the c.14576G>A (p.R4859K, rs112735431) variant in *ring finger protein 213* (*RNF213*; a gene located in chromosome 17q; based on the National Center for Biotechnology Information Reference sequence NP_065965.4), which is known to be a susceptibility gene for MMD.[14] Recently, *RNF213* c.14576G>A was reported to be associated with various phenotypes of intracranial major artery diseases.[18,19] We suggest that this genetic variant is associated with the repeated *de novo* aneurysm formation in the present case.

CASE REPORT

History and presentation
A 63-year-old male was admitted to Showa General Hospital with right hemiparesis. He had a history of hypertension, and no other risk factor of atherosclerosis. Magnetic resonance (MR) imaging revealed acute cerebral infarction in the left watershed area [Figure 1a], and MR angiography and digital subtraction angiography (DSA) demonstrated occlusion of the left ICA at the cervical portion [Figure 1b and c]. He was treated conservatively in the acute phase and scheduled for anastomotic surgery because technetium-99m-ethyl cysteinate dimer single photon emission computed tomography (^{99m}Tc-ECD SPECT) showed decreased cerebral blood flow.

First anastomosis and postoperative course
The patient underwent a left superficial temporal artery (STA)-middle cerebral artery (MCA) single anastomosis at the M4 portion with 15 sutures of 10-0 monofilament nylon [Figure 2a]. Postoperative DSA showed good patency of the anastomosis [Figure 1d], and ^{99m}Tc-ECD SPECT demonstrated improvement of cerebral blood flow. Postoperatively, the right hemiparesis improved with rehabilitation, and he was discharged without neurological deficit. First follow-up MR angiography with an interval of 2 years (due to transient lost follow-up) showed *de novo* aneurysm [Figure 1e].
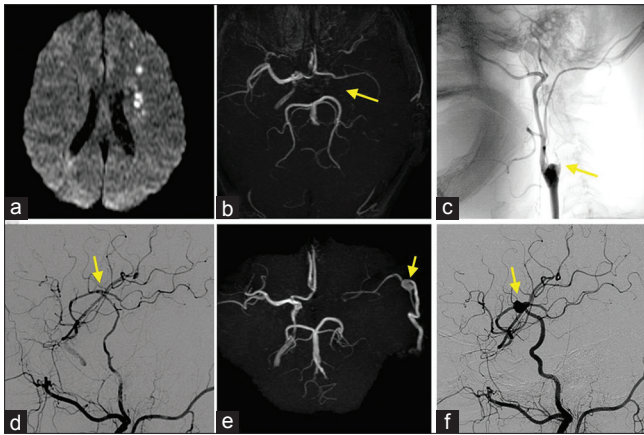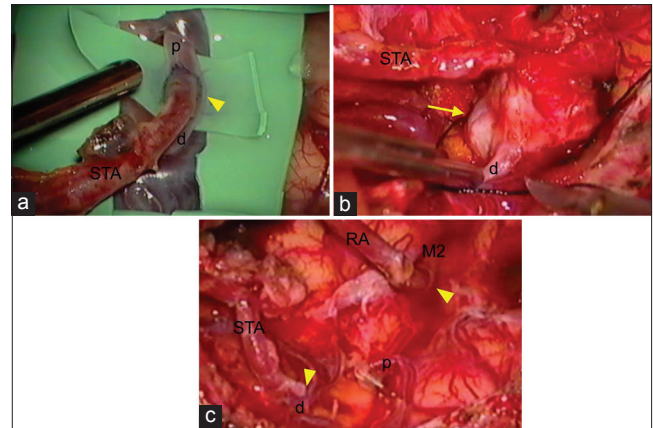
Figure 1: (a) Diffusion-weighted MR image at onset indicating acute watershed infarction due to hemodynamic insufficiency. (b and c) MR angiogram (b) and lateral DSA of the left common carotid artery (c) at the onset showing occlusion of the left ICA at the cervical portion (arrow). (d) Lateral DSA of the left common carotid artery after the first anastomosis in which the blood flow from the STA perfuses both proximal and distal to the anastomotic site (arrow). (e and f) MR angiogram (e) and lateral DSA of the left common carotid artery (f) performed 2.5 years after the first anastomosis showing *de novo* aneurysm at the anastomotic site (arrow)

Figure 2: (a) Intraoperative photograph of the first STA-MCA anastomosis (arrowhead). (b and c) Intraoperative photographs of the trapping of the aneurysm and second ECA-RA-M2 and STA-M4 anastomoses showing the *de novo* aneurysm (arrow) pretrapping view (b), and posttrapping and anastomoses (arrowhead) view (c). d : M4 portion of the MCA distal to the anastomosis; M2 : M2 portion of the MCA; p: M4 portion of the MCA proximal to the anastomosis; RA : Radial artery; STA : Superficial temporal artery

DSA performed 2.5 years after anastomosis (at the age of 66) revealed a 19.0-mm *de novo* saccular aneurysm at the anastomotic site [Figure 1f]. The left MCA territory was perfused mainly via the anastomosed STA, whereas cross flow via the anterior communicating artery, which had been detected immediately after anastomosis, had disappeared. He was scheduled for surgical intervention because the aneurysm was considered to be at high risk of rupture.

Second anastomosis

The patient underwent trapping of the aneurysm and left ECA-radial artery (RA)-MCA (M2 portion) and STA-MCA (M4 portion) anastomoses. Intraoperative findings showed that the *de novo* aneurysm at the anastomotic site had adhered to the superficial dura mater and the bottom brain surface with connective tissue. Clipping of the aneurysm was difficult, because the aneurysm was located exactly at the site of anastomosis [Figure 2b]. First, ECA-RA-MCA anastomosis was performed at the M2 portion to maintain perfusion of the MCA territory during the trapping procedure. Next, we resected the aneurysm, with ligation of the stump of the proximal M4. Finally, we performed anastomosis of the stumps of the STA and the distal M4 [Figure 2c]. Histological examination revealed that the aneurysm wall was thinned and consisted of collagen fibers, almost without media and internal elastic lamina, but immunohistochemistry revealed fragmented smooth muscle cells throughout the circumference, which established the diagnosis as true aneurysm [Figure 3]. Postoperative DSA showed good patency of the anastomoses [Figure 4a], and he was discharged without neurological deficit.
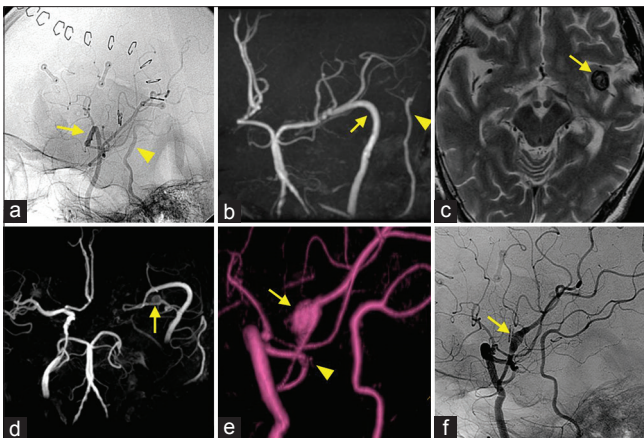
Postoperative course

Follow-up MR angiography showed good patency of the anastomoses and no other abnormal findings over the next 3 years [Figure 4b]. However, MR angiography 4 years after the second anastomosis (at the age of 70) demonstrated a dilatation of the left M3 portion that was remote from the ECA-RA-MCA anastomotic site. Follow-up MR angiography for 3 years showed that the dilatation enlarged gradually and became a 12.0-mm saccular aneurysm at the nonbranching site [Figure 4c-e]. Therefore, he was scheduled for DSA. DSA revealed a slightly dilated vessel, but the aneurysm lumen was not detected [Figure 4f]. These findings suggested that the aneurysm lumen was completely thrombosed, and had little risk of rupture. The last follow-up MR imaging showed no enlargement of the thrombosed aneurysm. The patient remains under observation without ischemic event or neurological deficit.

Genetic analysis and ethical considerations

The patient's son had been incidentally diagnosed with asymptomatic right MCA occlusion, so these craniocervical major artery diseases were suspected to have some association with genetic factors. The patient was referred to The University of Tokyo Hospital and genetic analysis was performed there as described previously.[18,19] Genetic analysis revealed the patient had *RNF213* c.14576G>A variant (heterozygote) [Figure 5]. The ethical reviews of the genetic analysis study in the two facilities (The University of Tokyo Hospital and Showa General Hospital) were both approved by the Human Genome, Gene Analysis Research Ethics Committee of the Faculty of Medicine, the University of Tokyo (approval number G10026-1). Written informed consent was obtained from the patient.
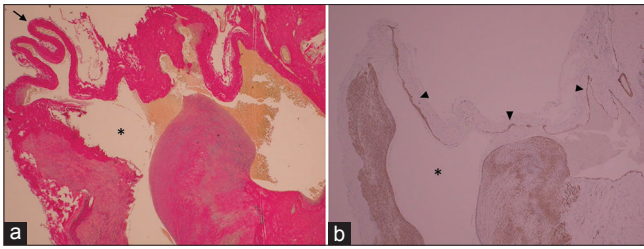
Figure 3: Photomicrographs of resected *de novo* aneurysm. Left: Wall of the aneurysm dome (arrow) is thinned and consisted of collagen fibers. Asterisk = aneurysm lumen. Elastica van Gieson stain, original magnification ×20. Right: Fragmented smooth muscle cells (arrowhead) are detected throughout the circumference. Alpha-smooth muscle actin stain, original magnification ×20

Figure 4: (a and b) Postoperative lateral DSA of the left common carotid artery (a) and follow-up MR angiogram (b) showing good patency of the ECA-RA-MCA (arrow) and STA-MCA (arrowhead) anastomoses. C–E: T2-weighted MR image (c) and MR angiograms (d and e) performed 6 years after the second anastomosis showing second *de novo* aneurysm located remote from the anastomotic site (arrow: Aneurysm, arrowhead: Anastomotic site) (f) Lateral DSA of the left common carotid artery exhibiting the dilated artery (M3 portion) without visualization of the aneurysm lumen (arrow)
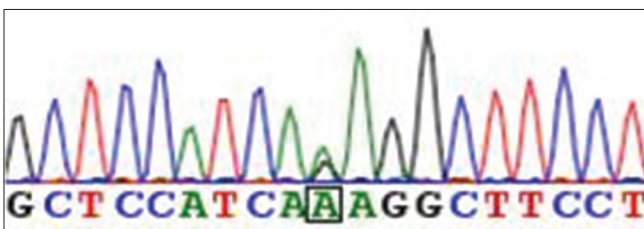
Figure 5: Sequencing chromatogram of the patient showing the heterozygote of the *RNF213* c.14576G>A variant

DISCUSSION

In the present case, the first *de novo* aneurysm at the anastomotic site was detected at 2.5 years after the STA-MCA anastomosis surgery, and was successfully resected with a pathological diagnosis of true aneurysm. The second *de novo* aneurysm located remote from the anastomotic site was detected at 4 years after the

ECA-RA-MCA anastomosis surgery, and was thrombosed naturally after gradual growth. This unique case represents repeated *de novo* aneurysm formation after ECA-ICA anastomosis. The extreme rarity of such repeated aneurysm formation and his family history suggested the involvement of genetic predisposing factors, leading us to identify the presence of the genetic variant *RNF213* c.14576G>A.

The genetic variant c.14576G>A in *RNF213* has significant associations with MMD and various phenotypes of non-MMD intracranial major artery stenosis and occlusion (ICASO).[14,18,19] This genetic variant is identified in about 80% of patients with MMD, and in 95% of patients with familial MMD.[17] In particular, this genetic variant is also found in about 20% of patients with non-MMD ICASO.[18,19] In contrast, the frequency of normal carriers is estimated at about 1–2% in East Asian population.[14,17] Due to such incomplete penetrance, *RNF213* is regarded as a susceptibility gene, so the existence of other triggering factors should be considered,[14,16] and the clarification of the physiological and biochemical functions of *RNF213* is important.

Vascular endothelial cells derived from induced pluripotent stem cells obtained from MMD patients carrying the *RNF213* variant had reduced angiogenic activities, and overexpression of *RNF213* variant in HeLa cells inhibited cell proliferation *in vitro*.[5,6] Accordingly, we speculate that the endothelial cells and smooth muscle cells were more vulnerable due to the genetic variant, so that increased hemodynamic stress due to the blood flow from the donor artery of the anastomosis resulted in *de novo* aneurysm formation in the present case.

We would refer to some limitations of this case report. First, the extreme rarity of the present case cannot be explained only by the presence of the genetic variant. STA-MCA anastomosis is a common surgical procedure for MMD and ICASO, and about 80% of patients with MMD and 20% of patients with ICASO had the genetic variant *RNF213* c.14576G>A.[18,19] Consequently, most carriers of genetic variant *RNF213* c.14576G>A who had undergone anastomosis did not develop *de novo* aneurysm. Second, the histological findings of the *de novo* aneurysm in the present case indicate atypical pathogenesis of occlusive arteries in MMD consisting of proliferative response of smooth muscle cells.[15] As triggering factors other than the genetic variant *RNF213* c.14576G>A are considered to be present in MMD, such other factors in addition to the genetic variant *RNF213* c.14576G>A were probably involved in the pathogenesis of the present case. Nevertheless, we believe that the present case represents an extremely rare phenotype of the genetic variant *RNF213* c.14576G>A.

CONCLUSION

The present extremely rare case of repeated *de novo* aneurysm formation after the first STA-MCA and second ECA-RA-MCA anastomoses occurred in a patient with the genetic variant *RNF213* c.14576G>A. We consider that the genetic variant was involved in the repeated *de novo* aneurysm formation, and this case represents a rare phenotype of the genetic variant *RNF213* c.14576G>A.

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