Vascular occlusion in a previously unaffected territory after treatment with intravenous plasminogen activator: illustrative case

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BACKGROUND Intravenous tissue plasminogen activator (IV t-PA) is effective for the treatment of distal artery occlusion. However, after the use of IV t-PA, vascular occlusion in unaffected territories may occur. Early recurrent ischemic stroke (ERIS) is defined as the occurrence of new neurological symptoms that suggest the involvement of initially unaffected vascular territories after intravenous thrombolysis (IVT). The authors reviewed the cases of ERIS that occurred within 24 hours after treatment with IVT.

OBSERVATIONS A 75-year-old woman with occlusion in the M2 segment of the left middle cerebral artery (MCA) was treated with IV t-PA. However, 360 minutes later, the patient presented with occlusion in the M1 distal segment of the contralateral side, the right MCA, which was recanalized by endovascular treatment. Her modified Rankin Scale score was 4; however, aphasia was not observed. She was transferred to a rehabilitation hospital after 3 months.

LESSONS ERIS is an extremely rare but catastrophic event. The underlying mechanism of ERIS most likely involves the disintegration and subsequent scattering of a preexisting intracardiac thrombus. Hence, caution must be used when managing not only hemorrhagic complications but also ischemic complications after IV t-PA. Endovascular management may be the only effective treatment for this type of large vessel occlusion.

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KEYWORDS tissue plasminogen activator; ischemic complication; endovascular treatment

Intravenous tissue plasminogen activator (IV t-PA) is effective for the treatment of distal artery occlusion.^{1,2} We present a case of occlusion in the M2 segment of the left middle cerebral artery (MCA) treated with IV t-PA. However, 360 minutes after treatment, the patient presented with occlusion in the distal M1 segment of the contralateral side, the right MCA, which was treated using the endovascular technique. Other cases of ischemic stroke with vascular occlusion in unaffected territories occurring within 24 hours of treatment with intravenous thrombolysis (IVT) were reviewed.

Illustrative Case

A 75-year-old woman with a history of diabetes mellitus and hyperlipidemia was admitted 20 minutes after the sudden onset of left hemiparesis and aphasia. Her National Institutes of Health Stroke Scale

(NIHSS) score was 23, and she presented with atrial fibrillation. Computed tomography (CT) scans on admission did not show any acute ischemic signs. Subsequent three-dimensional CT angiography revealed occlusion in the M2 segment of the left MCA (Fig. 1A). However, it did not reveal any stenoses or ulceration in the bilateral carotid artery of the cervical segment or any large plaques in the upper portion of the aortic arch. IV t-PA was administered 133 minutes after the onset of the event. Aphasia and level of consciousness gradually improved while the patient was in the intensive care unit, and her NIHSS score decreased to 8. However, 360 minutes after administration of IV t-PA, she experienced rightward conjugate deviation and left hemiparesis, and her NIHSS score increased to 38. Emergency diffusion-weighted imaging revealed an acute ischemic lesion in the right corona radiata and a small ischemic lesion in the left hemisphere (Fig. 1B). Magnetic

ABBREVIATIONS CT = computed tomography; ERIS = early recurrent ischemic stroke; ICH = intracranial hemorrhage; IV t-PA = intravenous tissue plasminogen activator; IVT = intravenous thrombolysis; MCA = middle cerebral artery; mRS = modified Rankin Scale; MT = mechanical thrombectomy; NIHSS = National Institutes of Health Stroke Scale; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction; TICI = thrombolysis in cerebral infarction.

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FIG. 1. **A:** Three-dimensional CT angiography of the intracranial lesion revealed occlusion at the M2 segment of the left MCA (arrowhead). **B:** Diffusion-weighted imaging performed 6 hours after treatment with IV t-PA showed an acute ischemic lesion in the right corona radiata and a small ischemic lesion in the left hemisphere. **C:** Magnetic resonance angiography showed recanalization of the M2 segment of the MCA and occlusion in the M1 distal segment of the right MCA (arrowhead). **D:** The right internal carotid artery (ICA) angiogram revealed occlusion in the distal M1 segment of the MCA (arrowhead). **E:** Right ICA angiogram after thrombectomy revealed revascularization of the occluded MCA. **F:** Left ICA angiogram showed no residual stenosis of the M2 segment of the MCA after treatment with IV t-PA.

resonance angiography showed recanalization of the M2 segment of the MCA and occlusion in the M1 distal segment of the right MCA (Fig. 1C). The patient was then referred for endovascular treatment because the event occurred after treatment with IV t-PA. Angiography revealed occlusion in the M1 distal segment of the right MCA (Fig. 1D). The Penumbra System 5MAX ACE and 3MAX catheters were used to navigate the M1 segment of the MCA. The aspiration catheter of 5MAX could easily navigate the M1 distal segment. The first aspiration via the 5MAX removed the thrombus, and thrombolysis in cerebral infarction (TICI) grade 3 revascularization of the affected MCA territory was achieved (Fig. 1E). A left internal carotid artery angiogram also showed TICI grade 3 revascularization of the M2 segment of the left MCA (Fig. 1F). Magnetic resonance imaging performed on the day after admission revealed infarctions in the right MCA territory and small infarctions in the left MCA territory. The patient's modified Rankin Scale (mRS) score was 4; however, aphasia was not observed. She was transferred to a rehabilitation hospital 3 months later.

Discussion

According to Georgiadis et al.,³ early recurrent ischemic stroke (ERIS) is defined as the occurrence of new neurological symptoms

that suggest the involvement of initially unaffected vascular territories and evidence of corresponding ischemic lesions on cranial CT scans in the absence of intracranial hemorrhage (ICH). To the best of our knowledge, only 10 cases exist,⁴⁻⁷ including 2 case series^{3,8} of ERIS occurring within 24 hours after treatment with IVT (Table 1). In those 2 case series, the incidence rates of ERIS were 0.59%³ and 2.6%.⁸ In most cases, ERIS occurred within 60 minutes after treatment with IVT. However, no relationship seemed to exist between the site of the first occlusion and the second. Seven cases involved patients with an mRS score of 6 with conservative therapy. The present study involves the third case in which the patient survived and was treated with an endovascular technique. The first patient was treated with intraarterial thrombolysis, which resulted in an mRS score of 6;⁸ the second patient was treated with endovascular aspiration, which resulted in an mRS score of 4.⁴ That study was written in the Japanese language, however.

The underlying mechanism of ERIS after treatment with IVT for acute ischemic stroke most likely involves the disintegration and subsequent scattering of preexisting intracardiac thrombus.^{3,9} The source of the embolism in our patient's second event may have been related to the preexisting intracardiac thrombus. However, in

TABLE 1. Eleven cases of ERS within 24 hours after treatment with IVT

Case No.	Author & Year	Age (yrs), Gender	Risk Factor	Site of First Occlusion	Onset to Initial t-PA (mins)	Site of Second Occlusion	Initial t-PA to Second Occlusion (mins)	Treatment	Image	Outcome
1	Kissela et al., 2001 ⁵	80, F	AF	Rt M1 distal susp	165	BA distal susp	120	Cons	BA occlusion	Death
2	Lai & Hu, 2006 ⁶	81, M	AF, HT	Rt M1 proximal susp	120	Lt M1 proximal susp	62	Cons	Bilat MCA infarction	ND
3	Georgiadis et al., 2006 ³	72, M	HT, DM	Lt ICA susp	170	Rt M1 proximal, rt PICA	40	Cons	Multiple infarction	Death
4	Georgiadis et al., 2006 ³	78, F	HT	Lt M1 proximal susp	175	Lt ICA, rt ICA	50	Cons	Bilat MCA infarction	Death
5	Yalcin-Cakmakli et al., 2009 ⁷	75, F	AF, CHF, HT, HL	Lt M1 distal	ND	Rt ICA, lt anterior cerebral artery	59	Cons	Lt MCA, rt ICA	mRS 5
6	Awadh et al., 2010 ⁸	80, F	AF, IHD	Lt MCA	160	BA	80	ET	BA occlusion	Death
7	Awadh et al., 2010 ⁸	64, F	HT	Rt MCA	210	Lt MCA	60	Cons	Bilat MCA infarction	Death
8	Awadh et al., 2010 ⁸	62, M	AF, HOCM	Lt MCA	165	Rt MCA	45	Cons	Bilat MCA infarction	Death
9	Awadh et al., 2010 ⁸	74, M	DM, IHD	Lt MCA	150	ND	40	Cons	Lt MCA, rt PCA	Death
10	Hanakawa et al., 2017 ⁴	82, F	AF	Rt M1 distal susp	210	Lt MCA distal	55	ET	Bilat basal ganglia	mRS 4
11	Present case	75, F	AF	Lt M2	133	Rt M1 distal	360	ET	Lt multiple, rt MCA	mRS 4

AF = atrial fibrillation; BA = basilar artery; CHF = chronic heart failure; Cons = conservative treatment; DM = diabetes mellitus; ET = endovascular treatment; HL = hyperlipidemia; HOCM = hypertrophic obstructive cardiomyopathy; HT = hypertension; ICA = internal carotid artery; IHD = ischemic heart disease; ND = not described; PCA = posterior cerebral artery; PICA = posterior inferior cerebellar artery; susp = suspected site of the occluded vessel based on the images in the papers.

the acute setting for stroke management, it may be impossible to evaluate the size and fragility of a thrombus in the heart. Embolic stroke is a well-recognized event, but it rarely occurs in patients undergoing IVT for acute myocardial infarction.⁹⁻¹¹ The incidence rate was reported to be between 0.4% and 0.7% during hospital stay.¹² Primary percutaneous coronary intervention (PCI) is defined as coronary angioplasty/stenting without prior IVT for ST-elevation myocardial infarction (STEMI).^{13,14} In the early 2000s, primary PCI was considered more effective in treating STEMI than IVT.¹⁴ The primary PCI protocol seemed to be standard management for STEMI in the 2010s in Japan.¹⁵

It is widely accepted that IV t-PA is particularly effective in the treatment of distal artery occlusion.^{1,2} Now, however, neurointerventionalists can safely perform procedures on smaller and distal arteries using new devices for endovascular therapy.^{2,16} A meta-analysis of mechanical thrombectomy (MT) for the M2 segment of the MCA reported that the rate of IV t-PA received before MT was 57%, the symptomatic ICH rate was 16%, and the recanalization rate of TIC1 grade 2b/3 was 81%.¹⁶ Takagi et al. reported that the administration of preprocedural IV t-PA did not increase the incidence of ICH in total; however, it

increased the incidence of symptomatic ICH in patients with M2 occlusion.¹⁷ The "IV t-PA skip and direct MT method," also referred to as "primary MT," may be a treatment option for M2 occlusion. In our patient, the occurrence of this rare ischemic event and hemorrhagic complications associated with IV t-PA might have been prevented.

Observations

Only 10 cases of ERS occurring within 24 hours after treatment with IV t-PA have been noted. ERS is an extremely rare but catastrophic event. The underlying mechanism of ERS most likely involves the disintegration and subsequent scattering of preexisting intracardiac thrombus. Hence, caution must be used when managing not only hemorrhagic complications but also ischemic complications after treatment with IV t-PA. Endovascular management may be the only effective treatment for this type of large vessel occlusion.

Lessons

IV t-PA may cause ERS, which is an extremely rare but catastrophic event. Caution must be used when treating not only

hemorrhagic complications but also ischemic complications after treatment with IV t-PA. Endovascular management may be the only effective treatment for this type of large vessel occlusion.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Sugie, Yamada, Miyake, Ito, Tanaka, Nomura, Fujita, Nakatani, Kawanishi. Acquisition of data: Sugie, Miyake, Ito, Tanaka, Nomura, Fujita, Nakatani. Analysis and interpretation of data: Sugie, Miyake, Ito, Tanaka, Nomura, Fujita, Nakatani. Drafting the article: Sugie, Ito, Tanaka, Nomura, Kawanishi. Critically revising the article: Sugie, Miyake, Ito, Tanaka, Nomura, Fujita, Nakatani. Reviewed submitted version of manuscript: Sugie, Ito, Tanaka, Nomura, Nakatani, Kawanishi. Approved the final version of the manuscript on behalf of all authors: Sugie. Statistical analysis: Ito, Tanaka, Nomura. Administrative/technical/material support: Sugie, Miyake, Ito, Tanaka, Nomura, Fujita, Nakatani. Study supervision: Sugie, Yokoyama, Ito, Tanaka, Nomura, Kawanishi.

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