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Case Report

A Case of Internal Carotid Artery Restenosis Due to Neointimal Hyperplasia Following Balloon Angioplasty

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Objective: The causes of restenosis following balloon angioplasty are reported to be vasospasm, thrombosis, and recurrence of atherosclerosis. We report a case of internal carotid artery (ICA) occlusion treated by emergency endovascular renacalization and carotid endarterectomy (CEA) for the restenosis, which revealed that the cause of restenosis was neointimal hyperplasia.

Case Presentation: A 70-year-old man was brought to our hospital because of sudden onset left hemiparesis. His National Institute of Health Stroke Scale (NIHSS) score was 13. Magnetic resonance imaging diffusion weighted imaging (MRI DWI) demonstrated hyper-intensity in the right basal ganglia, indicating acute ischemia. Neither the right ICA nor the MCA was visualized on MR angiography. Following intravenous tPA therapy, endovascular treatment was employed. First, the right ICA occlusion was treated by balloon angioplasty and the right M1 occlusion was recanalized by the stent-type thrombus retriever. Complete recanalization was achieved and the patient fully recovered. However, restenosis of the right ICA developed 5 months later and CEA was performed. The postoperative course was uneventful. Based on the pathological examination, the cause of restenosis was migration and proliferation of dedifferentiated smooth muscle (SM) cells, that is, neointimal hyperplasia.

Conclusion: Neointimal hyperplasia can be a cause of restenosis following balloon angioplasty.

Keywords ▶ carotid artery stenosis, balloon angioplasty, restenosis, neointimal hyperplasia

Introduction

Etiological factors for restenosis following balloon angioplasty or stenting for carotid artery stenosis include vasospasm, thrombosis, and recurrent atherosclerosis. On a patient with right internal carotid artery (ICA) and middle cerebral artery (MCA) occlusion who was brought to our hospital by ambulance with cerebral infarction, we performed balloon angioplasty and conducted carotid endarterectomy (CEA) for restenosis after 5 months. Pathological examination of the extirpated specimen demonstrated subintimal proliferation of the tissue continuing from the vascular media. Transformed smooth muscle (SM) cells were identified as the component of the lesion by immunostaining. We present this patient with a literature review of restenosis after balloon angioplasty.

Case Presentation

Patient: A 70-year-old male.

Weakness of the left half body suddenly developed. He was brought to our hospital by ambulance. He had a history of hypertension; he had received drug therapy. He had smoked 20 cigarettes/day. Mild consciousness disorder, left hemiplegia, and conjugate deviation of the right eye were observed. The National Institute of Health Stroke Scale (NIHSS) score was 13. Diffusion-weighted cephalic magnetic resonance imaging (MRI) demonstrated a light high-signal-intensity area in the right basal ganglia (**Fig. 1A**). On magnetic resonance (MR) angiography, neither the right ICA nor the right MCA was visualized (**Fig. 1B**). The right ICA was occluded at its origin (**Fig. 1C**). A diagnosis was made within 4.5 hours after onset, and intravenous

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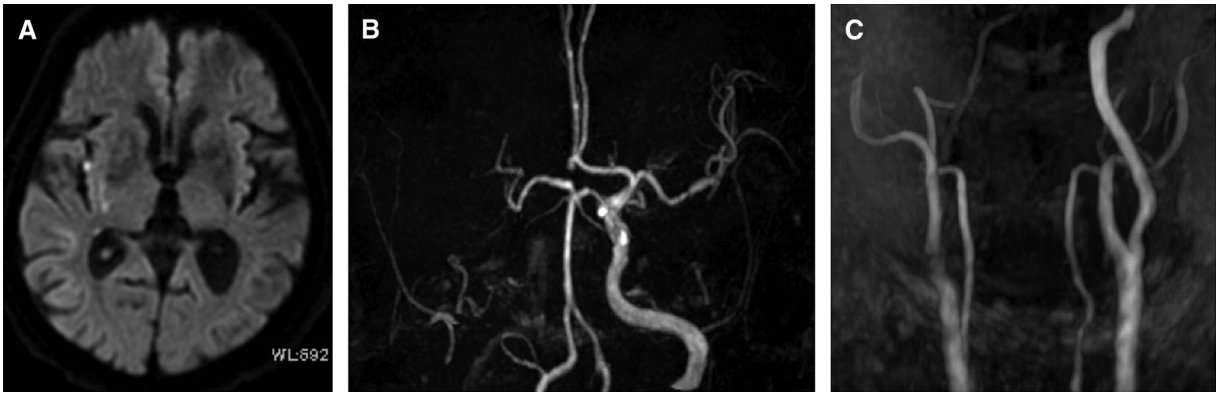

Fig. 1 Initial MRI. (**A**) DWI shows a high-intensity lesion in the right basal ganglia and right frontal lobe, indicating acute ischemic lesion. (**B**) Neither the right ICA nor MCA was visualized on intracranial MR angiography. (**C**) Cervical MR angiography revealed occlusion of the right ICA. DWI: diffusion weighted imaging; ICA: internal carotid artery; MCA: middle carotid artery; MRI: magnetic resonance imaging

thrombolysis with tissue plasminogen activator (tPA) was performed. Endovascular recanalization therapy was subsequently conducted.

Neuroendovascular treatment

Under local anesthesia, a 9-F sheath was inserted into the left femoral artery and a 9-F Optimo guiding catheter (Tokai Medical, Aichi, Japan) was inserted into the right common carotid artery. A thrombus was aspirated by dilating the balloon of the guiding catheter, leading to slight recanalization. Marked stenosis was noted at the origin of the ICA (**Fig. 2A**). Using a 0.014 guidewire, a Coyote 4.0 mm × 30 mm balloon catheter (Stryker, Natic, MA, USA) was guided to the site of stenosis, and dilated at 6 atmospheric pressures for vasodilation (**Fig. 2B**). Distal angiography confirmed occlusion of the M1 portion of the right MCA (**Fig. 2C**). A Marksman microcatheter (Covidien, Dublin, Ireland) was guided to the M2 region and angiography was performed. The periphery of the MCA was visualized (**Fig. 2D**). A Solitaire 6 mm × 40 mm (Covidien) was deployed to collect thrombi. A large volume of thrombi was adhered to the stent. Angiography confirmed TICI IIb recanalization of the M1 region (**Fig. 2E**). Additional treatment for stenosis at the origin of the ICA was conducted. Using a Sterling balloon catheter 5 mm × 30 mm (Stryker), vasodilation was performed at 8 atmospheric pressures. Improvement was achieved (percent stenosis: approximately 50%) (**Fig. 2F**). After 15 and 30 minutes, angiography was repeatedly conducted to confirm the absence of stenosis progression or a delay in blood flow. The procedure was completed. The interval from onset until hospital arrival was 1 hour and 3 minutes. That from hospital arrival until intravenous thrombolysis with tPA was 1 hour and 16 minutes. That from arrival until puncture was 1 hour and 59 minutes. That from puncture until recanalization was 41 minutes. That from onset until recanalization was 3 hours and 43 minutes.

Postoperative course

After surgery, the neurological symptoms almost improved. Diffusion-weighted cephalic MRI demonstrated scattered punctiform high-signal intensities in the bilateral cerebral hemispheres (**Fig. 3A**). On MR angiography, the right ICA and MCA were favorably visualized (**Fig. 3B**). Computed tomography (CT) angiography revealed moderate eccentric stenosis at the origin of the right ICA (**Fig. 3C**). For follow-up, the patient was referred to a rehabilitation hospital. The oral administration of amlodipine at 5 mg was continued, and aspirin at 100 mg and clopidogrel at 75 mg were added. The patient was instructed to comply with smoking cessation. Carotid ultrasonography 5 months after discharge revealed restenosis, and CT angiography confirmed restenosis at the origin of the right ICA (**Fig. 4**). The site of restenosis was isoechoic on ultrasonography, and high- and low-brightness areas were mixed in a portion. T1-weighted high-resolution MRI demonstrated an iso-signal. Considering the risk of recurrent cerebral infarction, CEA was performed. Under general anesthesia, monitoring was conducted using the somatosensory-evoked potential and topical oxygen saturation. The bifurcation of the right common carotid artery was exposed, and the blood vessel was clamped. There was a decrease in cerebral blood flow, and the stenotic lesion was extirpated using an internal shunt and used as a pathological specimen. After surgery, there were no neurological abnormalities. CT angiography confirmed that stenosis of the right

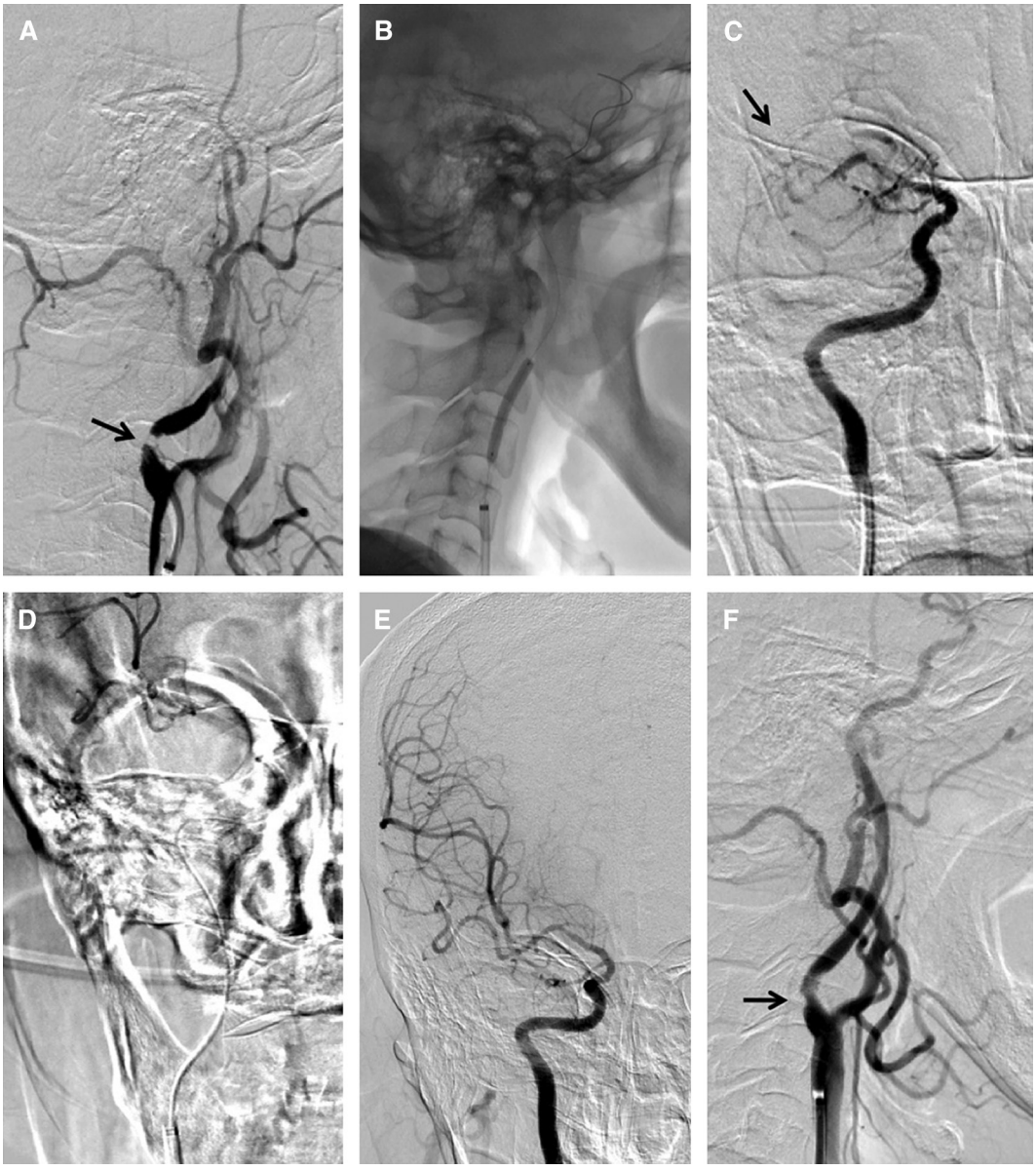

Fig. 2 Endovascular treatment. (**A**) Lateral view of right carotid angiography following aspiration via the balloon-guiding catheter shows high-grade stenosis at the origin of the ICA (arrow). (**B**) Lateral view of the non-subtracted image of the balloon angioplasty for ICA stenosis. (**C**) A-P view of right carotid angiography after angioplasty revealed right MCA occlusion, indicating a tandem lesion. (**D**) A-P view of selective angiography with a microcatheter shows patency of the distal portion of the MCA. (**E**) A-P view of right carotid angiography following retrieval of the thrombus shows recanalization of the MCA. (**F**) Lateral view of right carotid angiography following balloon angioplasty shows residual stenosis at the right ICA (arrow). ICA: internal carotid artery; MCA: middle carotid artery

ICA had improved (**Fig. 5**). During the 1-year follow-up after CEA, the condition has been favorable.

Pathologically, the tissue continuing from the media of the vascular wall had invaded the subintimal area, causing lumen stenosis (**Fig. 6A**). At this site, the dense proliferation of hematoxylinophil fusiform cells was observed (**Fig. 6B**). On α-SM actin staining, a positive reaction, which originated from SM cells, was detected (**Fig. 6C**). However, desmin staining was negative (**Fig. 6D**), suggesting transformed SM cells. A diagnosis of neointimal hyperplasia was made.

Discussion

Stenosis at the origin of the ICA induces cerebral ischemia related to blood flow disorder, leading to acute occlusion through plaque rupture or a tandem lesion related to artery-to-artery embolism. In such cases, emergency treatment

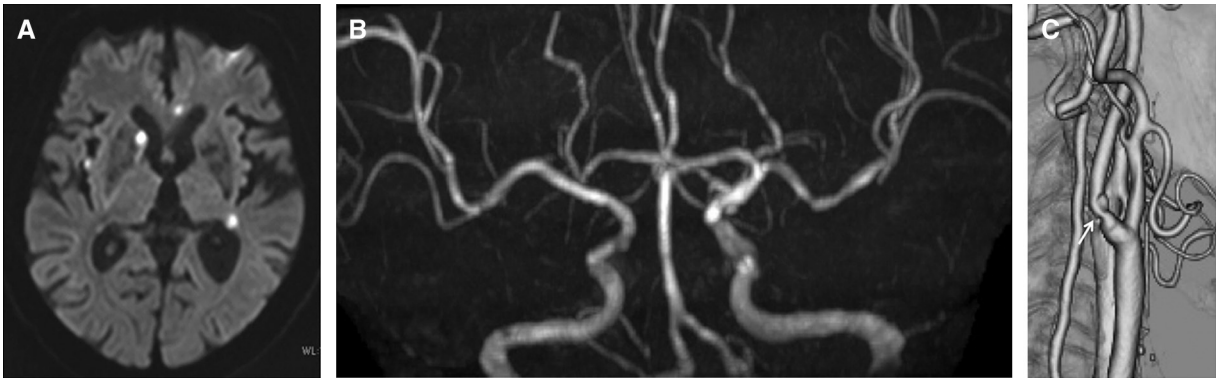

Fig. 3 Postprocedural imaging studies. (**A**) DWI shows a high-intensity lesion in the bilateral cerebral hemisphere. (**B**) MRA shows complete recanalization of the right MCA. (**C**) CT angiography shows mild residual stenosis at the origin of the right ICA (arrow). CT: computed tomography; DWI: diffusion weighted imaging; ICA: internal carotid artery; MCA: middle carotid artery; MRA: magnetic resonance angiography

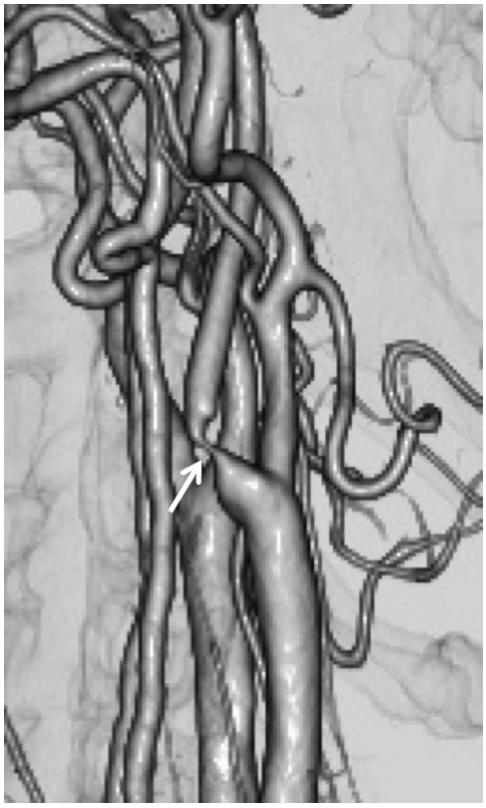

Fig. 4 CT angiography 5 months later. Restenosis was revealed at the origin of the right ICA (arrow). CT: computed tomography; ICA: internal carotid artery

Fig. 5 Postoperative CT angiography. The right ICA stenosis was sufficiently dilated. CT: computed tomography; ICA: internal carotid artery

has been increasingly required. Intracranial emboli must be collected, but there are two treatment options for lesions at the origin of the ICA: (1) balloon angioplasty is performed, followed by radical treatment after the condition becomes stable and (2) one-stage carotid artery stenting (CAS).[1] For one-stage CAS, it is necessary to use two antiplatelet drugs after surgery; this may lead to hemorrhagic infarction. Therefore, if possible, two-stage treatment is adopted. For two-stage treatment, CEA is selected in the absence of risk factors.[2] In the present case, sufficient dilation was achieved on initial balloon angioplasty and follow-up was conducted. After 5 months, restenosis was noted. As the

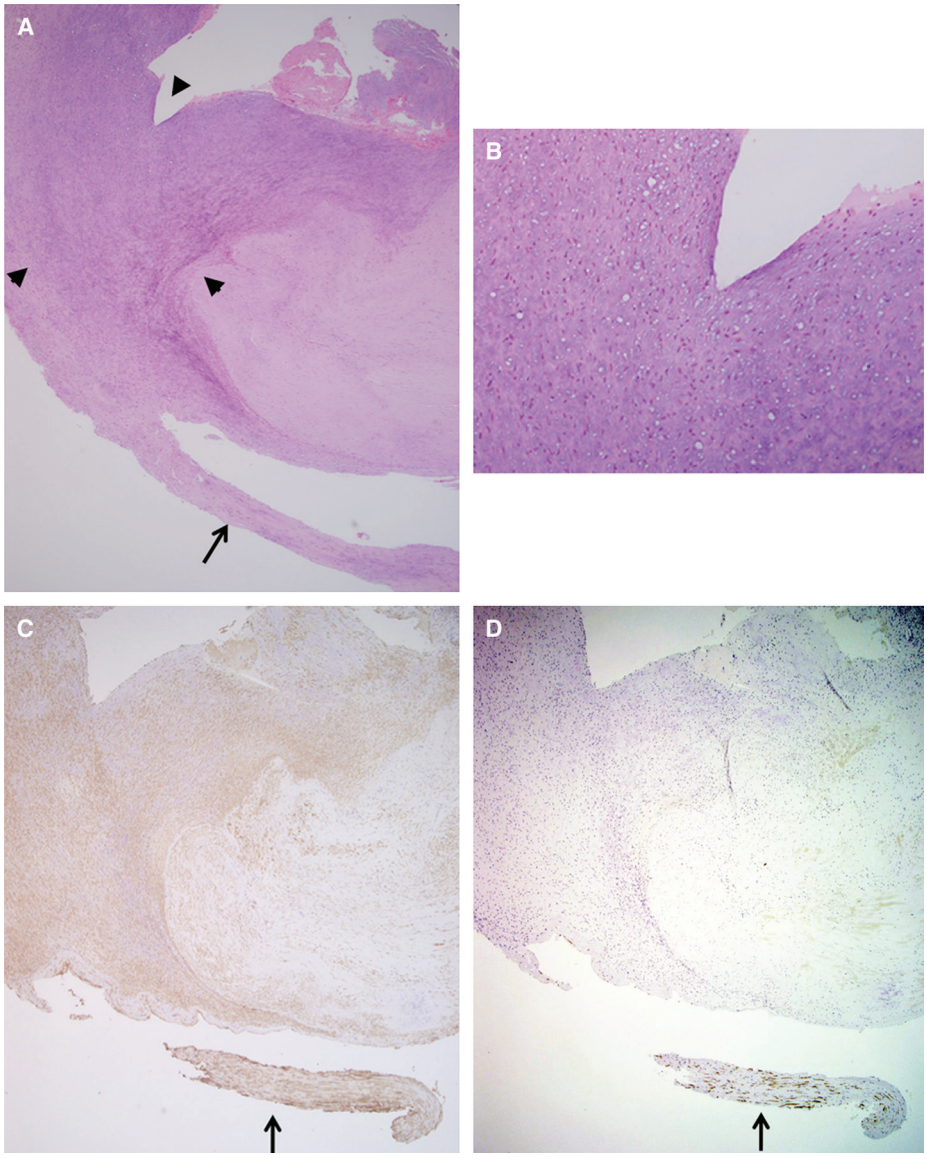

Fig. 6 Histopathological study. (**A**) H&E staining shows infiltration of cells from vascular media (arrow) to the subintima (arrowhead). Original magnification ×50. (**B**) Hyper-magnification of A shows proliferation of fusiform cells with high cellularity. Original magnification ×200. (**C**) Immunohistochemistry is positive for α-SM actin, indicating vascular SM cells. The vascular media is stained positive as a positive control (arrow). Original magnification ×100. (**D**) Immunohistochemistry is negative for desmin, indicating dedifferentiation of the SM cells. The vascular media is stained positive as a positive control (arrow). Original magnification ×100. H&E: hematoxylin and eosin; SM: smooth muscle

plaque was considered to be unstable, with marked changes, that is, history of plaque rupture and restenosis, CEA was performed.

Restenosis following vasodilation may be related to elastic recoiling or thrombus formation if the interval until restenosis is short. Restenosis after a ≥2-year period of follow-up may be associated with recurrent atherosclerosis. Based on pathological examination of resected specimens, the lesion primarily consisted of transformed SM cells.[3] The vascular SM is classified as the synthetic type at the level of genesis. It functions in angiogenesis through migration, proliferation, and secretion of growth factors or extracellular matrix. After angiogenesis, it differentiates into the contraction type, primarily functioning in vascular pulsation or elasticity. In the presence of endothelial dysfunction-related stimuli, cell growth factors are secreted by monocyte-derived macrophages invading an area below the damaged intima or platelets aggregating at the site of intimal exfoliation, and the medial SM cells stimulated by these factors migrate from the media and proliferate. The

SM cells lose their differentiation characteristics and pass through the internal elastic membrane while proliferating, thus migrating to the subintimal layer. Through further proliferation, they gradually induce intimal thickening while secreting the extracellular matrix.[4] In atherosclerotic lesions, transformed SM cells have also been observed and a previous study examined these cells as an etiological factor.[5] The phenotype of SM cells can be differentiated by immunostaining of muscle fibers or cell adhesion molecules.[6] In the present case, the vascular media was positive for α-SM actin and desmin (contraction type). The cells involved in stenosis were positive for α-SM actin, but were negative for desmin despite the SM system (synthetic type).[7] This condition is termed neointimal hyperplasia and it may also be a repair response to angiopathy.

Previously, neointimal hyperplasia was investigated as an etiological factor for restenosis after coronary artery stenting.[8] To prevent this, a drug-eluting stent was developed.[9] We previously reported a patient in whom stenting for stenosis at the origin of the vertebral artery was performed and restenosis was evaluated using intravascular ultrasonography.[10] For CAS, neointimal hyperplasia is also indicated as an etiological factor for restenosis, but the diameter of the carotid artery is relatively wide and neointimal hyperplasia is not problematic.[11] Furthermore, hyperplasia reduces after a specific period and partial fibrosis may lead to regression. Therefore, close follow-up is necessary. In the present case, acute occlusion initially developed and neointimal hyperplasia was observed after balloon angioplasty. The inflammatory reaction was also etiologically involved in the neointimal hyperplasia. The presence of acute occlusion due to the plaque rupture, in this case, indicates inflammatory reaction may be more marked than chronic lesions.

If T1-weighted plaque MRI and ultrasonography demonstrate an iso-signal and uniform equiluminance, respectively, the possibility of neointimal hyperplasia may be high.[10] Neointimal hyperplasia is a fibromuscular lesion, and it may not induce plaque rupture or plaque internal bleeding. If the degree of stenosis is low, follow-up should be performed. If marked stenosis is noted, blood flow disorder may develop and treatment is necessary. In the present case, stenosis became marked and surgical treatment was considered to be necessary.

Conclusion

We reported a patient with restenosis 5 months after balloon angioplasty for carotid artery occlusion. Neointimal hyperplasia was etiologically involved in restenosis.

This research was recommended by the Japanese Society for Neuroendovascular Therapy in 2019.

Disclosure Statement

The authors declare no conflict of interest.

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