A Case of Carotid Artery Stenosis Complicating Scleroderma Treated by Carotid Artery Stenting

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Objective: We treated a patient with carotid artery stenosis complicating scleroderma by carotid artery stenting (CAS) and achieved satisfactory dilation. Since scleroderma was suspected to have induced carotid artery stenosis, we report the case with a review of the literature.

Case Presentation: The patient was a 75-year-old woman diagnosed with scleroderma 8 years before. She thereafter developed polymyositis, liver cirrhosis, and stenosis of the bilateral internal carotid arteries; as progression of stenosis was observed, treatment was considered necessary. In consideration of the patient’s general condition, CAS by the transbrachial approach was selected. There was no complication associated with the procedure, and satisfactory dilation could be achieved. No restenosis was observed 6 months after the procedure. The history of previous disorders and the results of antibody tests strongly suggested scleroderma as a cause of carotid artery stenosis.

Conclusion: We performed CAS in a patient with carotid artery stenosis suspected to have been caused by scleroderma and obtained a favorable outcome.

Keywords: scleroderma, carotid artery stenting, carotid artery stenosis

Introduction

Scleroderma is a connective tissue disease with unknown etiology. Its primary symptoms include Raynaud’s phenomenon, sclerosis of the skin of peripheral, occasionally central, parts of the extremities, and lung and kidney disorders, but there have also been reports of stenosis of large vessels such as the pulmonary, carotid, and femoral arteries, and its pathological features are diverse.1–10 Carotid artery stenting (CAS) is being established as a treatment for carotid artery stenosis complicating arteriosclerosis obliterans and generalized arteriosclerosis, but reports on its effectiveness and prognosis in carotid artery stenosis associated with scleroderma are few. In this report, we present a patient who underwent CAS for carotid artery stenosis suspected to have been induced by scleroderma and showed a favorable outcome.

Case Presentation

The patient was a 75-year-old woman. She was found to have asymptomatic bilateral carotid artery stenosis and was referred to our hospital in 200X. She had been diagnosed with scleroderma 8 years before and with polymyositis 4 years before. Scleroderma was definitively diagnosed to be limited cutaneous systemic sclerosis (lcSSc) because anti-centromere antibody was positive, and dermal sclerosis was observed but was localized distally to the elbow. Despite a history of diabetes and liver cirrhosis, diabetes was controlled adequately by insulin therapy and oral
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medication. Since gradual progression of stenosis was noted during outpatient follow-up for carotid artery stenosis, she was admitted for treatment in 200X+6.

She had a history of diabetes, intervertebral disc hernia, liver cirrhosis, angina pectoris (percutaneous coronary angioplasty using drug-eluting stents was performed in 200X-5 and 200X-4), vascular stenosis of the lower extremities (percutaneous angioplasty using stents was performed in the right common iliac artery in 200X+1 and in the right femoral and left common iliac arteries in 200X+5), rectal varices (sclerotherapy was performed in 200X+3), and portal hypertension (transjugular intrahepatic portosystemic shunt was performed in 200X+6).

Her familial history included death of her older and younger sisters due to tuberculosis. There was no history of smoking or drinking.

At presentation, she was 149 cm tall and weighed 50 kg (body mass index [BMI] = 22), had a clear sensorium, and showed no neurological abnormalities. Thickening and pallor of the skin of the bilateral fingers and dermal scleroderma localized distally to the elbow were noted.

On diagnostic imaging, cervical MRA demonstrated moderate stenosis of the left carotid artery and marked stenosis of the right carotid artery (Fig. 1). Black blood MRA showed carotid artery plaques that were isointense on T1-weighted imaging and partially hyperintense on

Fig. 1 (A) Right common carotid MRA shows internal carotid artery stenosis at the origin on February 200X. (B) Right common carotid MRA shows prognosis of internal carotid artery stenosis on October 200X+6.

Fig. 2 (A) Black blood T1-weighted MRI revealed isointense plaque in the right internal carotid artery. (B) Black blood T2-weighted MRI revealed a hyperintense area in isointense plaque.
Plt was $70 \times 10^3$/mm$^3$ (normal: 140–350), prothrombin time (PT) was 13.3 seconds (normal: 10.5–13.5), prothrombin activity was 72.3% (normal: 70.0–130.0), PT-international normalized ratio (PT-INR) was 1.18 (normal: 0.76–1.27), activated partial thromboplastin time (APTT) was 27.2 seconds (normal: 25.0–40.0), T-cho was 163 mg/dL (normal: 150–219), high-density lipoprotein cholesterol (HDL-cho) was 46 mg/dL (39–93), low-density lipoprotein cholesterol (LDL-cho) was 94 mg/dL (normal: 70–139 mg/dL), triglyceride (TG) was 113 mg/dL (normal: 50–149), and hemoglobin A1c (HbA1c) was 5.4% (normal: 4.6–6.2), indicating mild anemia and thrombocytopenia. There was no dyslipidemia, the HbA1c level was normal, and diabetes was controlled adequately.

On special examinations, anti-centromere antibody was positive, and anti-Jo-1 antibody, anti-GAD antibody, T2-weighted imaging (Fig. 2). On 3D-CTA, calcification was noted in parts of the stenosed area, and ultrasonography of the carotid arteries presented stenotic lesions accompanied by calcification in the bilateral carotid arteries. Stenosis of the right carotid artery was severe, isoechoic to hyperechoic plaques were observed, the extent of stenosis was 56% by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method, 87% by the European Carotid Surgery Trial (ECST) method, and 75% by the area method, and the peak systolic velocity was 280 cm/s (Fig. 3). On cerebral angiography, also, general vascular tortuosity and progression of stenosis compared with the findings in 200X were confirmed on the right side (Figs. 4 and 5).

Concerning the blood test results, RBC was $303 \times 10^4$/mm$^3$ (normal: 380–480), Hb was 10.0 g/dL (normal: 11.5–14.9),
anti-mitochondrial antibody, and anti-cardiolipin antibodies were negative.

Since stenosis rate increased (from 50% to 56% by the NASCET method, from 64% to 87% by the ECST method, and from 38% to 75% by the area method) despite oral antiplatelet therapy (clopidogrel at 75 mg/day) during a 6-year follow-up period, the condition was judged to be an indication for revascularization. As thrombocytopenia due to liver cirrhosis was observed, carotid endarterectomy (CEA) was considered to involve the risk of cervical...
subcutaneous hematoma formation, and CAS was selected. CAS was decided to be performed by the transbrachial rather than transfemoral approach because of the history of treatment for stenotic lesions in the right femoral and bilateral common iliac arteries.

For endovascular treatment, oral administration of aspirin at 100 mg/day was initiated 10 days before the procedure in addition to 75 mg/day clopidogrel that had already been administered. A 6 Fr guiding sheath (ASAHI Fubuki dilator kit: Asahi Intecc, Aichi, Japan) was placed in the right common carotid artery via the right brachial artery. With distal protection using a balloon system (PercuSurg; Medtronic, Minneapolis, MN, USA), pre-dilation was performed using a 4.0 mm × 30 mm balloon (Sterling, Stryker, Kalamazoo, MI, USA), and PRECISE 8 mm × 30 mm (Cordis, Miami, FL, USA) was placed. Post-dilation was performed using a 4.5 mm × 20 mm balloon (Aviator; Cordis), and 60 mL of blood was aspirated using an aspiration catheter. No debris was confirmed. The protection balloon was deflated, and the procedure was ended by confirming adequate dilation and the absence of plaque protrusion by intravascular ultrasound (IVUS) (Fig. 6).

Post-procedurally, intravenous drip infusion of argatroban at 60 mg/day was maintained for 2 days, and its intermittent administration was sustained for 3 days by splitting 20 mg/day into two doses. Oral administration of 75 mg/day clopidogrel and 100 mg/day aspirin was continued. There were no periprocedural complications, and no restenosis was noted on carotid artery ultrasonography performed half a year after the procedure.

Discussion

Scleroderma is a systemic connective tissue disorder characterized by skin and visceral fibrosis and vasculopathy. Vasculopathy includes not only regional circulatory disturbance due to contraction of arterioles and small arteries of the fingers and toes called Raynaud’s phenomenon, but also intimal proliferation or fibrotic thickening of the media.\(^1\)\(^2\)\(^5\)

There have also been sporadic reports concerning macrovascular disorders complicating scleroderma although their frequency is lower than peripheral vasculopathy such as Raynaud’s phenomenon.\(^1\)\(^2\)\(^5\) Veale et al. reported that the incidence of intermittent claudication is higher in patients with scleroderma than in the general population and that, in such patients, scleroderma is often complicated by cardiovascular and cerebrovascular ischemic events.\(^2\) Indeed, in our patient, coronary artery stenosis was followed by common iliac artery and femoral artery stenosis and, subsequently, by carotid artery stenosis. Therefore, the possibility of the occurrence of ischemic events in the cerebrovascular system must be kept in mind. Reductions in elastic force and vascular compliance of the common carotid artery, which is an elastic artery, have also been
reported in patients with scleroderma, and they are considered to be results of arteriosclerosis and fibrotic vascular stenosis caused by intimal proliferation and fibrotic thickening of the media. As for the decrease in elastic force of the common carotid artery, the vascular wall compliance is significantly reduced in scleroderma patients even after adjustment for age, gender, BMI, heart rate, blood pressure, cardiovascular load, and creatinine, cholesterol, triglyceride, and blood sugar levels, and altered fibrillin-1 metabolism associated with a defect in chromosome 15q has been suggested as an etiological factor. In addition, the carotid intima-media thickness (IMT) in scleroderma patients was reported to be unrelated to common risk factors of arteriosclerosis. These reports suggest direct involvement of scleroderma in macrovascular disorders.

Furthermore, in lcSSc, in which dermal sclerosis is localized distally to the elbow, anti-centromere antibody is positive, and, despite a relatively favorable life prognosis, the frequency of the occurrence of macrovascular lesions is higher with many reports of marked stenosis or occlusion of large vessels. Progression of stenosis is considered to be accelerated by a close involvement of anti-centromere antibody in an increase in platelet activity, damage of vascular endothelial cells, vascular contraction, and hypercoagulability. The condition of our patient, who was positive for anti-centromere antibody and showed localized dermal sclerosis, was in agreement with lcSSc.

In our patient, generalized vascular tortuosity and progression of stenoses were demonstrated by intracranial angiography, and the black blood technique presented findings suggestive of soft plaques. Therefore, changes due to arteriosclerosis and fibrotic vascular stenosis are considered to have coexisted with enhanced platelet activity and thrombotic stenosis due to damage to vascular endothelial cells.

However, the patient also had a history of diabetes, which is a common risk factor of arteriosclerosis, evaluation of arteriosclerosis obliterans was also necessary. Disorders generally considered to be closely related to arteriosclerosis include diabetes and hyperlipidemia, but our patient showed a normal HbA1c level, indicating that diabetes had been adequately controlled over a long period. Moreover, she had no disorders that occur due to prolonged poor control of diabetes such as diabetic retinopathy, nephropathy, and peripheral neuropathy. There was also no hyperlipidemia, no risky lifestyle such as smoking and drinking, obesity, or dietary intemperance, and no factor suspected to be related to arteriosclerosis was observed. Since she developed multiple and progressive stenotic disorders in large vessels including the coronary, common iliac, femoral, and carotid arteries despite the low-risk state, an involvement of scleroderma was considered most likely. We considered general changes due to fibrotic vascular stenosis associated with scleroderma and the action of anti-centromere antibody to be the core pathology of our patient.

Ueda et al. reported a case of scleroderma complicated by arteriosclerosis obliterans and suggested that it is necessary to consider arteriosclerosis obliterans as a possible complication if there are risk factors such as diabetes and hyperlipidemia or unilateral progression of lesions. However, their case was negative for anti-centromere antibody unlike our case. They also suggested that the effect of scleroderma should be considered if there are obstructive changes in bilateral lower limb arteries, and this applies to our case.

Among other factors related to scleroderma that affect large vessels, an involvement of anti-cardiolipin antibody in thrombosis of large vessels has been suggested in anti-cardiolipin-positive patients (those with anti-phospholipid antibody syndrome), but this antibody was negative in our patient.

Renard et al. reported a patient who showed progressive thrombosis during anticoagulant medication and developed carotid artery embolization and called for attention to a hypercoagulable state in scleroderma patients. The same report presented a rapid clinical course of anti-centromere-antibody-positive lcSSc. Some scleroderma patients were reported to have developed angiitis of vessels of the central nervous system including the carotid artery, and angiitis is also considered a mechanism involved in macrovascular stenosis. In these reports, cerebral angiography demonstrated diffuse stenosis of cervical to intracranial vessels. Presenting a patient who exhibited rapid progression of cerebral infarction on the day of admission and died after 1 month, Lee et al. reported that the autopsy findings that no cell infiltration was noted in fibrotic tissue that proliferated in the carotid artery and that inflammatory changes were observed in connective tissues around the vasa vasorum, carotid artery, and proximal middle cerebral artery suggest angiitis and pointed out that impairment of the central nervous system in scleroderma patients is often assumed to be related to kidney disorders or hypertension because of its rareness. Fournier et al. reported the patient who developed transient neurological symptoms and suspected an involvement of vasospasm of the central nervous system because changes in vascular reactivity are observed in conditions including Raynaud’s phenomenon, nephropathy, and
cardiac dysfunction as physiological characteristics in scleroderma patients. Rapid clinical courses were reported in the above patients who showed conditions such as a hypercoagulable state, angiitis, and vasospasm unlike our patient, in whom vascular stenosis progressed over a period of 6 years, but they should be remembered in the differential diagnosis of cerebrovascular disorders in scleroderma patients.

Concerning the treatment, revascularization was considered necessary as the disease progressed with internal treatment alone. CEA and CAS were possible options, but CAS was selected as there was thrombocytopenia due to liver cirrhosis, and the risk of cervical subcutaneous hematoma formation after CEA was expected.

Liver cirrhosis has also been reported to be related to scleroderma. Primary biliary cirrhosis (PBC) is observed in 15.6% of scleroderma patients, and 5.8% of them are negative for anti-mitochondrial, anti-SP100, and anti-GP210 antibodies. Since PBC can be diagnosed from clinical symptoms and biopsy findings, it cannot be excluded even if anti-mitochondrial antibody is negative as in our patient. Particularly, PBC has been suggested to occur frequently with lcSSc positive for anti-centromere antibody. Patients with no history of drinking, such as our patient, tend to be diagnosed with liver cirrhosis due to non-alcoholic fatty liver, but the possibility of PBC should be sufficiently taken into consideration.

As for the approach for CAS, we avoided the transfemoral approach as the patient had been previously treated for bilateral common iliac artery stenosis and evaluated direct puncture of the carotid artery, transbrachial approach, and transradial approach as alternatives. Direct puncture of the carotid artery was excluded due to the risk of cervical subcutaneous hematoma formation. By the transbrachial approach, despite the risk of ischemia and nerve entrapment syndrome due to prolonged compression after the procedure, the lesion can be approached from a more proximal vessel, which ensures better manipulability, than by the transradial approach. By the transradial approach, while the risk of access site complications can be reduced, complications associated with insertion of a 6 Fr guiding sheath, such as vasospasm and vascular occlusion, may occur. In our patient, the transbrachial approach was selected because we attached priority to the manipulability since the common carotid artery arose from the subclavian artery at a very sharp angle, and because we wanted to avoid unexpected occlusion of the radial artery despite a positive Allen’s test since there was a report that the ulnar artery, in particular, shows more advanced stenosis than other vessels in scleroderma patients. The patient showed adequate post-procedural vessel dilation (Fig. 6) and no puncture site hematoma or procedural complications.

Reports on CAS in scleroderma patients are few. In one case that we could review, CAS rather than CEA was selected due to skin induration in the neck. Although the procedure was performed with distal protection using Angioguard (Cordis), the no-reflow phenomenon was reported to have occurred in the filter device. In our patient, we performed CAS using a balloon-type embolic protection device and could achieve a favorable outcome without thromboembolic complications.

### Conclusion

We treated a patient with carotid artery stenosis suspected to have been induced by scleroderma. A favorable outcome could be achieved by CAS via the transbrachial approach using a balloon-type embolic protection device.

### Disclosure Statement

There are no conflicts of interest to disclose concerning this paper.

### References


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