〈Case Report〉

Cholesterol crystal embolization after staged angioplasty for severe carotid artery stenosis

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ABSTRACT **Objective**: Staged angioplasty is an effective and safe carotid revascularization technique that avoids complications associated with postoperative cerebral hyperperfusion syndrome. Cholesterol crystal embolization (CCE) is a rare but severe complication of interventional and surgical procedures. Here in, we report on a patient with cholesterol crystal embolization who underwent staged angioplasty for severe carotid artery stenosis.

Case Report: A 72-year-old man with chronic kidney disease and dyslipidemia presented with left-sided homonymous hemianopsia. MRI showed an acute cerebral infarction in the right occipital lobe, and cerebral angiography confirmed severe right internal carotid artery stenosis. We planned a staged angioplasty for carotid artery stenosis owing to concerns about postoperative cerebral hyperperfusion syndrome because preoperative single-photon emission CT showed decreasing cerebral blood flow on the affected side. Staged angioplasty was performed smoothly; however, after treatment, the patient developed worsening chronic renal failure, immense pain in the right fifth toe, and livedo extending from the toes to the plantar surface on both feet. Skin biopsy confirmed the presence of cholesterol crystal embolization, owing to which he was required to receive dialysis and undergo toe amputation.

Conclusion: Because staged angioplasty requires multiple catheter operations, careful attention must be paid to the occurrence of cholesterol crystal embolization. To our knowledge, this is the first report of a rare complication associated with staged angioplasty.

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Key words：Angioplasty, Carotid stenosis, Cholesterol crystal embolization, Rare complication

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INTRODUCTION

Cerebral hyperperfusion syndrome (CHS) is a rare but potentially fatal complication of carotid artery stenting (CAS) or endarterectomy (CEA) in patients with severe carotid artery stenosis. Staged angioplasty is a delayed carotid artery stenting procedure after angioplasty for severe internal carotid artery (ICA) stenosis. Yoshimura, *et al*. first demonstrated its usefulness in preventing postoperative CHS[1]. Currently, its usefulness is widely recognized[2, 3], and we have actively adopted staged angioplasty for cases of severe ICA stenosis where the cerebral blood flow observed on preoperative resting single-photon emission CT (SPECT) is reduced.

Cholesterol crystal embolization (CCE) is caused by the occlusion of small arteries by cholesterol crystal emboli from major atherosclerotic arteries. CCE can cause multiple organ dysfunction, including dysfunction of the skin, kidneys, gastrointestinal tract, and central nervous system[4]. Most of which have shown that CCE can occur spontaneously. However, a few reports mention iatrogenic complications of CCE from angiography or vascular surgery[5]. We report on a patient who underwent a staged angioplasty for severe ICA stenosis and developed postoperative CCE. To our knowledge, this is the first report of a rare complication associated with staged angioplasty. Here, we report the clinical course of the disease and discuss its pathophysiology.

CASE REPORT

A 72-year-old man was referred to our department with left-sided homonymous hemianopsia. The patient was a regular smoker with a history of chronic kidney disease and dyslipidemia. He was taking six drugs including rosuvastatin (2.5 mg daily). Upon physical examination, his vital signs were within normal limits. The only neurological deficit was left homonymous hemianopsia. Laboratory analysis revealed chronic kidney disease (creatinine, 1.77 mg/dl, estimated glomerular filtration rate, 30.4 mg/min/1.73 cm^3), dyslipidemia (triglyceride, 163 mg/dl, high-density lipoprotein cholesterol, 38 mg/dl, low-density lipoprotein cholesterol, 98 mg/dl), and diabetes mellitus (glycated hemoglobin 6.7%). MRI revealed cerebral infarction in the right occipital lobe and severe right ICA. In addition, black-blood vessel wall MRI identified a high intensity signal in the root of the right ICA, suggesting an unstable carotid artery plaque. Cerebral angiography (transbrachial approach, using 25 ml of iopamidol) revealed that the rate of stenosis was 74%, as measured using the method mentioned in the North American Symptomatic Carotid Endarterectomy Trial (Fig. 1). Preoperative SPECT with N-isopropyl (123I) -p-iodoamphetamine showed that the cerebral

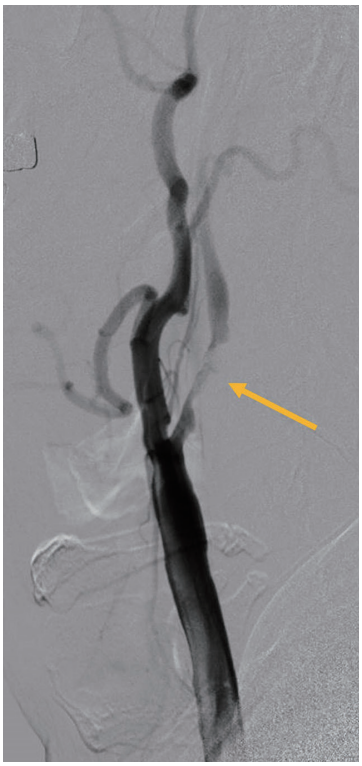

Fig. 1. Before staged angioplasty, angiogram showing severe stenosis of the right internal carotid artery (*arrow*).

blood flow on the affected side decreased to 85% of that on the unaffected side. We scheduled a staged angioplasty to minimize the risk of CHS. Unfortunately, the state of atherosclerosis along the access route from the puncture site to the carotid artery was not assessed using CTA or other methods. During first-stage angioplasty, we inserted a 9-Fr. sheath into the right common femoral artery and applied proximal protection of the 9-Fr. Mo. Ma Ultra device (Medtronic, Minneapolis, MN, USA), and distal protection was provided using Filter Wire EZ (Boston Scientific, Marlborough, MA, USA). The stenosis of the right ICA was dilated with a 2.5 × 40-mm SHIDEN balloon catheter (KANEKA MEDIX, Osaka, Japan) for 30 s at 8 atm, and the puncture site was closed with an 8-Fr Angioseal (TERUMO MEDICAL CORPORATION, Somerset, NJ, USA). A total of 35 ml of contrast medium (iopamidol) was used in the first-stage PTA. The post-operative course was uneventful, the patient was ambulatory and discharged. He complained of mild right toe pain but no new neurological symptoms. There was some deterioration in renal function (WBC 9,570 /mm^3, eosinophils 4.6%, UN 30 mg/dl, creatinine 2.96 mg/dl, eGFR 17.3 ml/min/1.73 m^2, CRP 1.32 mg/dl), but it was thought that this could be managed with fluid replacement. Therefore, he underwent second-stage carotid artery stenting 22 days after the first-stage angioplasty. We inserted a 9-Fr. sheath into the left common femoral artery, and provided proximal protection with 9-Fr. Mo. Ma Ultra device and distal protection with Filter Wire EZ. The stenosis was predilated with a 2.5 × 40-mm SHIDEN balloon catheter for 10 s at 8 atm. A 9 × 30-mm CASPER Rx (TERUMO, Tokyo, Japan), a self-expandable carotid stent, was deployed. The stent was dilated using a Sterling balloon dilation catheter (Boston Scientific, Marlborough, MA, USA) for 20 s at 12 atm. After dilation, the angiogram demonstrated favorable improvement (Fig. 2). The puncture site was closed using an 8-Fr Angioseal. A total of 27 ml of contrast medium (iopamidol) was used in the second-stage CAS. Immense pain in the right fifth toe and livedo extending from the toes to the plantar region on both feet appeared immediately after the

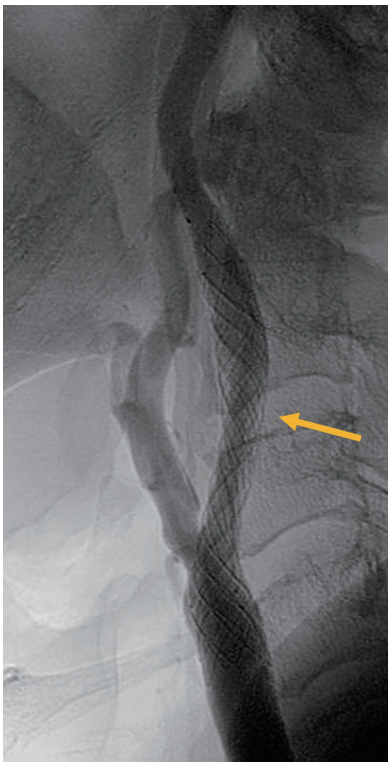

Fig. 2. After second-stage carotid artery stenting, angiogram showing favorable improvement (*arrow*).

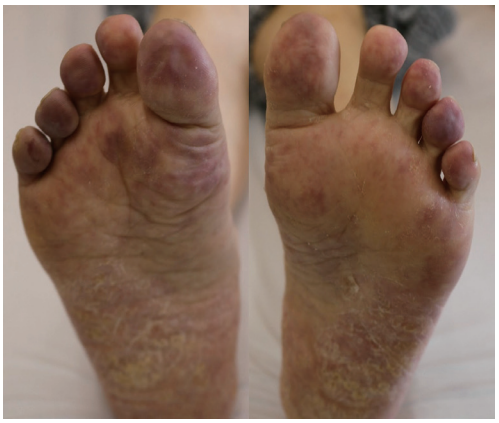

Fig. 3. Photograph showing blue toes on both feet, immediately after second-stage carotid artery stenting.

second-stage angioplasty (Fig. 3). Blood tests the day after treatment showed WBC 89,100 /mm^3, eosinophils 4.9 %, UN 28 mg/dl, creatinine 2.67 mg/dl, eGFR 19.4 ml/min/1.73 m^2, CRP 0.91 mg/dl, and adequate fluid replacement was continued. Blood tests 7 days later showed further deterioration of renal dysfunction (WBC 8,080 /mm^3, eosinophils 8.4%, UN 22 mg/dl, creatinine 3.22 mg/dl, eGFR 15.8 ml/min/1.73 m^2, CRP 3.79 mg/dl). A skin biopsy showed intravascular cholesterol clefts consistent with CCE (Fig. 4). Twenty-eight days after the first-stage angioplasty, the patient required dialysis induction. Furthermore, toe amputation was performed owing to necrosis of the bilateral toe tips on 94 days after the first-stage angioplasty (Fig. 5, 6).

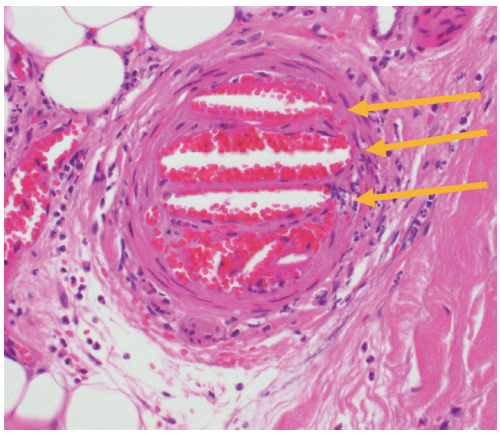

Fig. 4. Histologic slide of a skin biopsy specimen showing thrombotic occlusion and cholesterol crystals (*arrow*) in the arteriole.

DISCUSSION

CCE is well known to occur when aortic atherosclerotic plaques rupture owing to mechanical stimulation during angiography or vascular surgery, particularly percutaneous coronary intervention (PCI). In recent years, it has been recognized as a rare but serious complication following cerebrovascular interventions, such as carotid artery stent placement for ICA stenosis[6]. Some retrospective studies have reported that the estimated proportion of CCE cases after cerebrovascular procedures is 1.76 per 10,000 patients[7]. The significant risk factors for CCE reported in 23,183 patients who underwent PCI included abdominal aortic aneurysm, used of the femoral approach, age ≥ 70 years, and smoking history[8]. Our patient was considered at high risk for developing CCE because of his age and, smoking history, and

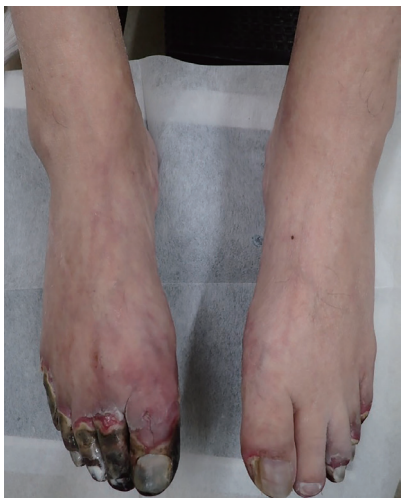

Fig. 5. Photograph showing necrosis of the bilateral toe tips 94 days after first-stage angioplasty.

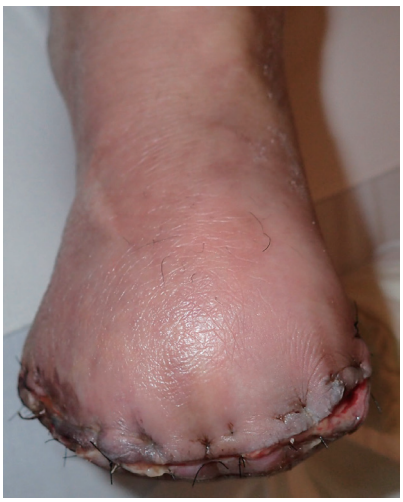

Fig. 6. Toe amputation performed for bilateral toe tip necrosis.

the endovascular procedure performed using the femoral approach.

Currently there is currently no standardized therapy for CCE. Statin therapy may cause plaque reduction and stabilization, significantly reducing the incidence of CCE, although it was not effective in our case. Additionally, a previous study reported that conventional steroid therapy with a proprotein convertase subtilisin / kexin type 9 inhibitor improves renal function and helps heals blue toes[9]. A prospective multicenter study of 34 patients reported that low density lipoprotein apheresis might help avoid the necessity for maintenance dialysis and is well tolerated in patients with CCE[10].

The prognosis of patients with CCE remains poor and treatment options are limited. Therefore, prevention of CCE onset is crucial. As staged angioplasty requires two catheter operations within a short period of time. In the case of CAS using MoMa, the device must be repeatedly passed through the access route because it is necessary to replace the catheter when guiding it to the common carotid artery. Therefore, our staged angioplasty using MoMa may have caused mechanical stimulation to the artery of the access route several times more than usual compared to simple CAS, which may have further induced CCE. Therefore, in this case, it was necessary to evaluate the arteriosclerosis state of the access route through which the catheter passes more thoroughly than usual before intervention. Aortic arch plaques should be evaluated using MRI / CTA of the aorta or transesophageal echography. If severe atherosclerosis of the aorta (shaggy aorta) is observed, access routes, such as the radial approach should be considered. If CCE is suspected after the first-stage angioplasty, it is imperative to halt or postpone staged angioplasty and focus on CCE treatment. For second-stage CAS, careful consideration should be given to whether the approach route should be changed to the radial artery or CEA should be considered.

In previous reports, the time from the causative event to the onset of CCE varied from < 1 day to 5 months[11]. Early symptoms of CCE may include minor complaints, such as lower extremity pain. Blood test findings include leukocytosis, transient eosinophilia, renal dysfunction, and elevated CRP. In our case, the patient complained of severe leg pain immediately after second-stage CAS, but only mild symptoms appeared after first-stage PTA. However, reviewing the blood test results showed that not only was renal dysfunction somewhat worse after the first stage PTA, but eosinophilia and CRP were also elevated. Mild CCE may have already occurred after the first stage PTA. Generally, the interval between the first PTA and second CAS is 2 to 4 weeks. It is crucial to document a patient's complaints after first-stage PTA and conduct a thorough evaluation through physical examination and blood tests to determine whether CCE has developed.

CONCLUSION

We have presented the first case of CCE with renal dysfunction, skin lesions, and ischemia of the toes following staged angioplasty for severe right ICA stenosis. Although CCE is a rare complication of CAS, treatment options are limited, and the prognosis remains poor. Staged angioplasty may be an effective method to prevent CHS. However, many patients with ICA stenosis who require staged angioplasty exhibit severe atherosclerosis, which is a risk factor for CCE. Staged angioplasty necessitates multiple catheterizations of the aorta, which may further increase the risk of CCE. Therefore, careful attention should be paid to the occurrence of CCE in such cases.

REFERENCES

1) Yoshimura S, Kitajima H, Enomoto Y, Yamada K, Iwama T: Staged angioplasty for carotid artery stenosis

to prevent post operative hyperperfusion. Neurosurgery. 2009; 64: 122-128.

2）Hayakawa M, Sugiu K, Yoshimura S, *et al.*: Effectiveness of staged angioplasty for avoidance of cerebral hyperperfusion syndrome after carotid revascularization. J Neurosurg. 2020; 132: 51-61.

3）Yoo DH, Roh HG, Choi SS, Moon J, Lee J, Cho YD, Han MH, Jung KH, Yoon BW, Kang HS.: Staged carotid artery stenting in patients with severe carotid stenosis: multicenter experience. J Clin Neurosci. 2018; 53: 74-78.

4）Shi C, Mammadova-Bach E, Li C, Liu D, Anders HJ.: Pathophysiology and targeted treatment of cholesterol crystal embolism and the related thrombotic angiopathy. FASEB J. 2023; 37.

5）Fukumoto Y, Tsutsui H, Tsuchihashi M, Masumoto A, Takeshita A.: The incidence and risk factors of cholesterol embolization syndrome, a complication of cardiac cathterization: a prospective study. J Am Coll Cardiol. 2003; 16: 211-216.

6）Pandit AK, Ohshima T, Kawaguchi R, Srivastava MP, Miyachi S.: Cholesterol embolization syndrome after carotid artery stenting associated with delayed cerebral hyperperfusion intracerebral hemorrhage. World Neurosurg. 2020; 142: 274-282.

7）Tanaka H, Yamana H, Matsui H, Fushimi K, Yasunaga H.: Proportion and risk factors of cholesterol crystal embolization after cardiovascular procedures: a retrospective national database study. Heart Vessels. 2020; 35: 1250-1255.

8）Takahashi K, Omuro A, Ohya M, Kubo S, Tada T, Tanaka H, Fuku Y, Kadota K.: Incidence, risk factors, and prognosis of cholesterol crystal embolism because of percutaneous coronary intervention. Am J Cardiol. 2022; 167: 15-19.

9）Tomoi Y, Soga Y, Imada K, Kodama K, Katsuki T, Hiramori S, Ando K.: Use of Proprotein Converse Subtilisin / Kexin Type 9 Inhibitor to Treat Cholesterol Crystal Embolisms after Catheterization: A Report of Three Cases. Intern Med. 2022; 15: 857-860.

10）Ishiyama K, Sato T.: Efficacy of LDL apheresis for the treatment of cholesterol crystal embolism: A prospective, controlled study. Ther Apher Dial. 2022; 26: 456-464.

11）Oe K, Araki T, Nakashima A, Nakashima A, Sato K, Konno T, Yamagishi M.: Late onset of cholesterol crystal embolism after thrombolysis for cerebral infarction. Intern Med. 2010; 49: 833-836.