Case Report: Massive Nasopharyngeal Bleeding during Endovascular Salvage for Subacute Stent Thrombosis in a Post-Radiation Patient

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Abstract

Carotid artery stenting (CAS) has been established as an alternative to endarterectomy (CEA) in radiotherapy-induced carotid stenosis, as prior cervical radiation increased surgical risk. Subacute stent thrombosis, although rare, may occur and result in catastrophic complication. We report a middle-aged patient, with radiotherapy-related symptomatic carotid stenosis, who succumbed to massive nasopharyngeal bleeding following endovascular salvage for subacute (3 weeks after carotid artery stenting) stent thrombosis. After symptomatic carotid stenosis was diagnosed, the patient received endovascular therapy successfully, however, subacute stent thrombosis developed. Further endovascular neurovascular salvage was performed with success, but the procedure was complicated by massive nasopharyngeal bleeding, hypotension, large cerebral infarction and death. Potential causes of subacute stent thrombosis might be the characteristics of the lesion and antiplatelet agent resistance. Massive nasopharyngeal bleeding might result from post-irradiation fragility of the vascular wall and balloon dilatation associated internal carotid artery rupture, potentiated by intra-arterial lytic therapy for neurovascular salvage. Bleeding events might be fatal after thrombolytic agent during endovascular salvage.

Keywords: radiotherapy, carotid stenosis, endovascular procedures, carotid artery thrombosis, hemorrhage

Introduction

Cervical radiotherapy plays an important role in head and neck cancer treatment. However, radiation causes progressive intimal hyperplasia and accelerates atherosclerosis in the affected area. Patients with high-degree carotid artery stenosis are at high risk for cerebral infarction. Carotid artery stenting (CAS) has been established as an alternative to endarterectomy (CEA), as prior cervical radiation increased surgical risk.[1] Unfortunately, subacute stent thrombosis, although rare, may occur and result in catastrophic complication.

We hereafter report a patient, with radiotherapy-related symptomatic carotid stenosis,

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who succumbed to massive nasopharyngeal bleeding following endovascular salvage for subacute (3 weeks after carotid artery stenting) stent thrombosis. The treatment courses and relevant literatures are reviewed.

Case Report

A middle-aged patient had a history of nonkeratinizing nasopharyngeal carcinoma (cT1N1M0, stage I) and he was treated by concurrent chemo-radiotherapy (CCRT) with radiotherapy dose at 70 Gy in 35 fractions in 2001 without recurrence. He underwent carotid artery stenosis evaluation in 2013 due to newly developed gait instability and slurred speech. He had presented with progressive left nasal obstruction and epistaxis 3 months prior his carotid artery lesions were identified. A growing left nasal cavity tumor which caused epistaxis was found by otolaryngologist. Magnetic resonance imaging (MRI) revealed a left nasal cavity lesion (36 x 32 mm) extending to the anterior ethmoid sinus without intracranial extradural extension. Left ethmoid sinusitis and left sphenoid sinus mucocele and hemorrhages were also noted. We performed tumor biopsy which revealed high-grade neuroendocrine carcinoma, T4aN2cM0 (minimal extension to cranial fossa, pterygoid plate), stage IVB. He was then treated with CCRT and the regimen was cisplatin. Total radiation dose was 60 Gy with a fraction dose of 2 Gy. He tolerated the treatment well with only mild left periorbital swelling, odynophagia, taste impairment, and leukopenia. His left nasal obstruction and epistaxis both resolved completely.

Two months after CCRT, he reported persistent oral cavity pain, headache, tinnitus, impaired hearing, and swallowing difficulty. Frequent choking resulted in several times aspiration pneumonia, and subsequent work-up revealed limited tongue motion and delayed/incomplete swallowing reflex. Progressive dizziness, impaired hearing, slurred speech, left vocal palsy with dysphonia, and gait instability were also noted. Follow-up MRI revealed no evidence of tumor recurrence, but carotid duplex ultrasonography showed left internal carotid artery (ICA) occlusion with reversed ophthalmic artery. Brain perfusion computed tomography (CT) confirmed the left ICA total occlusion (Figure 1A), and also documented significant right ICA stenosis at petrous segment (Figure 1B). Slightly prolonged mean transit time was noted in right middle cerebral artery territory (Figure 1C). Diagnostic angiography revealed 80% right ICA stenosis at upper cervical and petrous junction (Figure 2A). Left ICA total occlusion was also

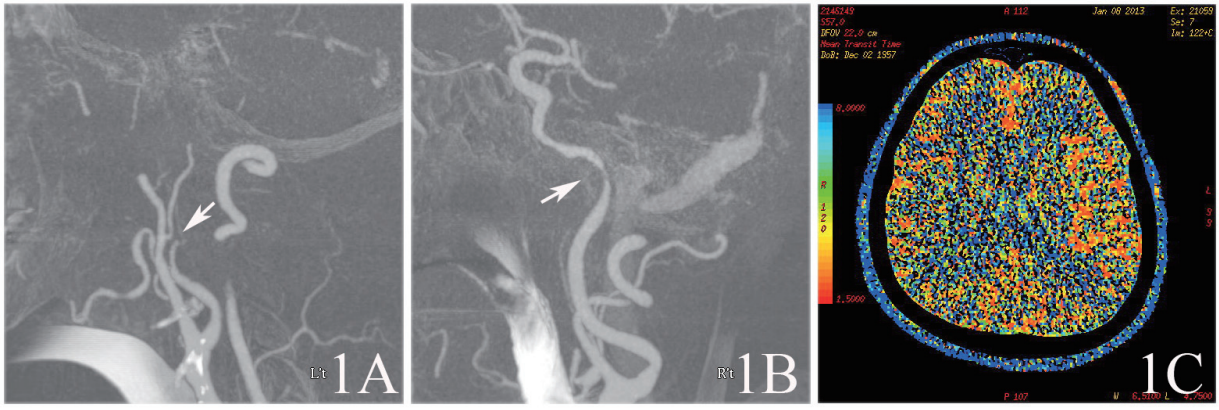

Figure 1. Pre-procedural computer tomography. Perfusion CT reveals left cervical ICA occlusion (arrow)(1A); Significant right internal carotid artery stenosis at petrous segment (arrow) (1B); Slightly prolonged mean transit time at right middle cerebral artery (MCA) territory (1C).

documented (Figure 2B), with distal reconstitution at the ophthalmic segment (Figure 2C). After detailed discussions about the treatment options with the patient, his family and our team members, we decided to perform endovascular intervention via the right femoral route. Heparin was given to achieve activated clotting time above 250 seconds, and right ICA stenting (PRECISE stent 7 x 40 mm, Cordis, California) was done uneventfully with embolic protection device (Figure 2D & 2E). We prescribed dual antiplatelet agents and he was discharged with stable condition.

Three weeks after endovascular procedure, sudden-onset left side weakness occurred, and he was sent to the emergency department immediately where brain CT revealed a long segmental thrombus, from right ICA origin to the cavernous portion (Figure 3A), causing total occlusion. The circle of Willis was intact (Figure 3B), but bilateral hemispheric hypoperfusion was noted. Subacute stent thrombosis was impressed, and emergent neurovascular salvage was performed. Cerebral angiography was done within 4 hours from symptom-onset time, showing right ICA stent thrombosis (Figure 4A) and distal ICA reconstitution via reversed ophthalmic artery (Figure 4B). As clot retrieval device was not available in Taiwan at that time, we performed thrombus aspiration with 7F Thrombuster II (Kaneka, Osaka, Japan), followed by angioplasty using Ikatzuchi balloon catheter (Kaneka) (angioplasty 4C). However, adequate

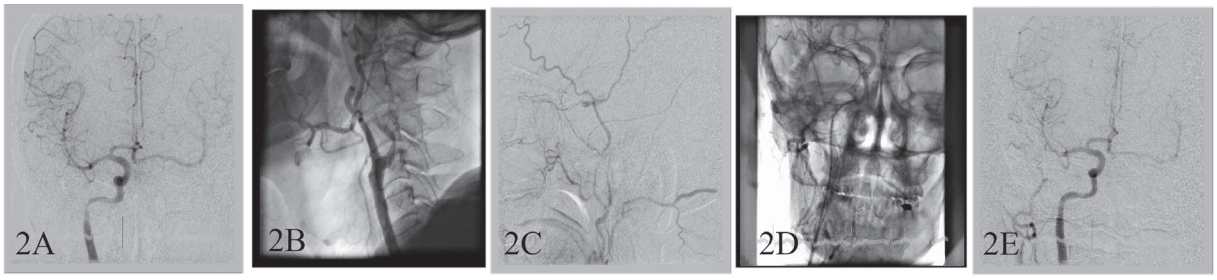

Figure 2. Endovascular therapy for right internal carotid artery stenosis. Cerebral angiography reveals right petrous ICA stenosis (2A), and left cervical ICA occlusion (2B) with distal reconstitution at ophthalmic segment (2C); Cordis PRECISE Stent 7 x 40 mm was deployed to cover the petrous ICA stenosis (2D); Final angiography reveals no residual stenosis (2E).

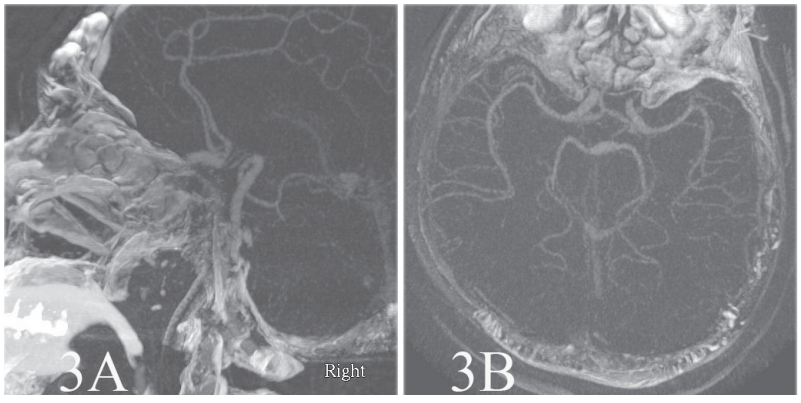

Figure 3. CT examination before endovascular neurovascular salvage. CT angiography reveals stent placement at cervical to proximal petrous segment of right ICA with long segmental thrombus and total occlusion of right ICA, from its origin to cavernous segment (3A); The circle of Willis is patent (3B).

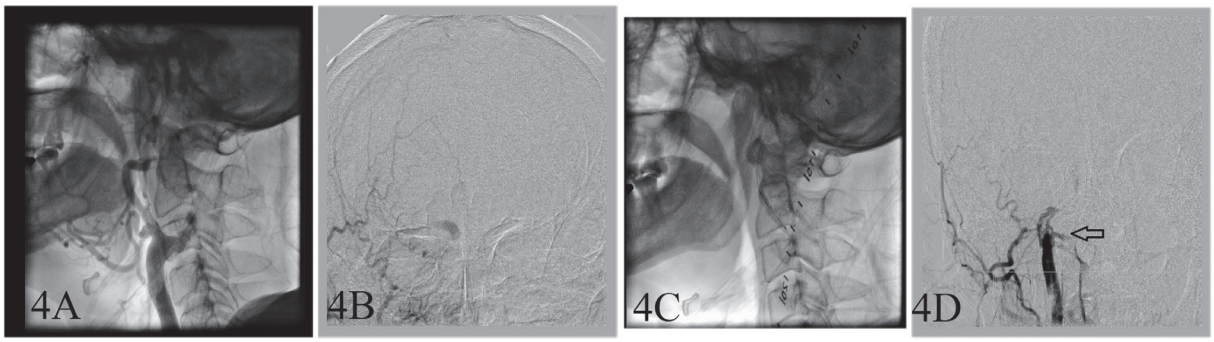

Figure 4. Neurovascular salvage for right carotid subacute stent thrombosis. Cerebral angiography shows total occlusion of right cervical ICA (4A); with distal reconstitution via reversed ophthalmic artery (4B); Dilatation with Ikatzuchi 2.5 x 15 mm balloon after thrombus aspiration (4C); Massive bleeding from distal cervical ICA (Black arrow) to nasopharynx after thrombolysis (4D).

antegrade flow was not established due to the extremely large thrombus burden. Intra-arterial thrombolysis was then given via microcatheter using recombinant tissue-type plasminogen activator (Actilyse, Boehringer Ingelheim, Germany). Distal flow increased to Thrombolysis in Cerebral Infarction (TICI) perfusion scale grade 2 after a total dose of 10 mg. Unfortunately, massive bleeding developed into oral and nasal cavities after thrombolysis, requiring endotracheal intubation and cardiopulmonary resuscitation. The bleeder was visualized by angiography, from upper cervical ICA into right nasopharynx (Figure 4D). Profound shock ensued despite vigorous fluid and component transfusion. The patient's consciousness also deteriorated. Local gauze packing with vasoconstrictor and foley balloon catheter tamponade were applied to the right side nasal cavity, but the bleeding continued. Brain CT revealed large infarction with mass effect at the right hemisphere, with multiple small foci of hemorrhagic transformation. The patient remained comatose and passed away five days later despite intensive management and hemodynamic support.

Discussion

The middle-aged patient we reported had a history of nonkeratinizing nasopharyngeal carcinoma and newly diagnosed left nasal high-grade neuroendocrine carcinoma. Symptomatic carotid artery stenosis was found after the second CCRT and he underwent subsequent endovascular therapy successfully. However, subacute stent thrombosis developed three weeks after carotid artery stenting. We performed endovascular neurovascular salvage immediately, but unfortunately, the procedure was complicated by massive nasopharyngeal bleeding, hypotension, large cerebral infarction and death. Several points merit discussion as follows.

The Relationship Between Radiation and Plaque Vulnerability/Vessel Fragility

The vulnerability of radiation-induced carotid stenosis (RICS) plaque has been a controversial issue. In current literatures, the researchers used several methods, including histologic analysis and image studies, to evaluate vulnerability in RICS plaque. The histologic analysis of Fokkema et al. revealed the tendency of RICS plaque to be stable. By contrast, several reports using carotid ultrasonography and magnetic resonance imaging but lacking histologic analysis have suggested a high incidence of vulnerable plaque in RICS patients.[2,3]

Radiation not only affects plaques but also causes vessel injury.[4,5] The effects include intimal proliferation, necrosis of the media, and fibrosis of the adventitia. We should always be cautious

when treating this kind of lesions, because interventional procedures themselves may cause further damage in an unfavorable vessel anatomy. In our opinion, the reasons for the patient's ICA bleeding might have been the radiation related vessel fragility and balloon dilatation-associated artery rupture.

Endovascular revascularization or endarterectomy

This patient received a total dose of 70 Gy radiotherapy for nasopharyngeal carcinoma in 2001, and another total dose of 60 Gy radiotherapy for left nasal high-grade neuroendocrine carcinoma in 2013. The development of carotid stenosis may be initiated by radiation therapy. The mechanism of radiation injury to the carotid artery includes direct and indirect components. The direct injury to the arterial wall leads to intimal proliferation, necrosis of the media, and fibrosis of the adventitia. Radiation also damages the vasa vasorum, causing indirect injury to the carotid artery with repetitive intra-plaque hemorrhages.[5] Surgical endarterectomy for radiation-induced carotid stenosis is associated with technical issues of arterial wall fibrosis, tissue plane scarring, potential prosthetic infection, anastomotic dehiscence, and surgically inaccessible distal or proximal lesion location. In addition, radiotherapy often causes bilateral stenosis or occlusion, sometimes rendering endarterectomy impossible.[6-8]

Therefore, carotid stenting has been considered as a reasonable alternative in radiation induced carotid stenosis.[4,8,9] However, due to the plaque vulnerability in radiation-related carotid stenosis, the risk of procedural embolism and subsequent in-stent thrombosis may be a concern.[10-12] In addition, in-stent restenosis rate was found higher in radiation induced carotid stenosis[4] than in non-radiated lesions. A systematic review comparing endarterectomy versus stenting for radiation induced carotid stenosis has shown that both techniques might be feasible, but there were more subsequent cerebrovascular events and restenosis in patients treated with stenting.[13] These findings probably reflect the progressive nature of radiation injury, despite aggressive control of cardiovascular risk factors.[4] Therefore, the choice of revascularization strategy should be individualized.

Potential causes of subacute cerebral infarction

As illustrated in Figure 1, critical stenosis with large plaque burden was located at the petrous portion of the right ICA, and the left ICA was totally occluded. Stenting was chosen, since endarterectomy would have been extremely difficult and risky. We used distal embolic protection device and performed endovascular intervention cautiously. Luckily the initial stenting procedure was successful without complication. However, the underlying vulnerable plaque might have protruded through the stent struts into the vessel lumen, leading to turbulent flow and thrombi formation. The choice of PRECISE stent, an open-cell stent with large cell size (free cell area: 5.89 mm^2), may have potentiated this effect. However, stent deliverability and vessel conformability would be another concern when deploying a closed-cell design stent to the petrous ICA.

Given that dual antiplatelet therapy plays an important role in carotid artery stenting, another potential cause for subacute stent thrombosis is antiplatelet drug resistance. In one study, regarding the prevalence of drug resistance in a Chinese population with minor stroke receiving dual antiplatelet therapy, 24.4% exhibited aspirin resistance, 35.9% exhibited clopidogrel resistance, and 19.2% displayed concomitant aspirin and clopidogrel resistance.[14] However, the rapid clinical deterioration prohibited further platelet function study on the patient in this case.

Neurovascular salvage

The patient arrived within 4 hours after stroke onset. CT scan and angiography both revealed stent thrombosis causing right ICA

occlusion. Using stent retriever to remove the clot has been shown to be effective in acute ICA occlusion,[15] but the device was unavailable at that time in Taiwan. Thrombus aspiration and balloon dilatation were performed, but the thrombus burden was too much to restore adequate flow. Intra-arterial heparin and recombinant tissue-type plasminogen activator were given according to prior protocol,[16] resulting in TICI 2 flow. Unfortunately, massive nasopharyngeal bleeding ensued, finally resulting in the demise of our patient. There was no evidence of local or intracranial tumor recurrence in his baseline imaging, but we did find extensive post-irradiation changes (mucosal thickening, mucus retention, and increased soft tissue density) in the patient's nasopharynx and paranasal sinuses. According to the radiation therapy record, the total cumulative radiation dose was extremely high and the field of the recent radiation was directed toward the ethmoid/sphenoid areas. Additionally, the interventional procedures themselves may have also caused further damage in an unfavorable vessel anatomy. Severe bleeding after intra-arterial lytic therapy most likely resulted from the radiation and procedure associated fragility of the vascular wall, surrounding soft tissue, and the proximity of the distal cervical ICA to the nasopharyngeal cavity. Despite mechanical tamponade using gauze and balloon compression in the nasal cavity, the hemorrhagic shock still resulted in massive ischemic stroke in this unfortunate patient with bilateral carotid disease.

Covered stents in the carotid circulation are mainly used for repair of aneurysm, pseudoaneurysm, dissection, perforation and arteriovenous fistula.[17,18] Several literatures have also reported the experiences of covered stent usage in carotid blowout syndrome and transsphenoidal surgery associated ICA rupture. We can take covered stent into consideration if bleeding or vessel injury event occurs. However, the designs of covered stents are rigid, with relatively large crossing profiles, making the procedure challenging at the petrous portion of ICA.

Strategy of revascularization in symptomatic patients with high surgical risk

In the latest American Heart Association/ American Stroke Association (AHA/ASA) guidelines (updated in 2014),[19,20] it is recommended to choose CEA over CAS in symptomatic patients at average or low surgical risk (Class I). But there is no definite recommendation for selection of revascularization in symptomatic patients at high surgical risk. The criteria for being classed as "high risk for CEA" include one or more of: clinically significant cardiac disease, severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal nerve palsy, recurrent stenosis after CEA, previous radical neck surgery or radiation therapy to the neck, and age > 80 years. According to this guideline (Class IIa recommendation), it is reasonable to choose CAS over CEA when patients have unfavorable neck anatomy (including post-irradiation changes) for arterial surgery.

Therefore, We have tried to report the varied conditions and difficulties during revascularization with CAS in our high-surgical-risk patient. And more, we hope that this unfortunate clinical course can help further research to clarify the appropriate treatment recommendation in symptomatic and high-surgical-risk group in the future.

Conclusion

We reported a patient who twice received extensive radiotherapy for head and neck malignancies and developed severe symptomatic carotid artery stenosis. Carotid stenting was initially successful, but subacute stent thrombosis occurred three weeks later. Intra-arterial lytic therapy restored TICI 2 flow, but was complicated by massive nasopharyngeal bleeding and led to patient death. Management in patients with radiation induced carotid artery disease should be tailored individually, considering their unique pathology.

Disclosure Statement

All authors have no conflict of interest.

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