Repeated massive epistaxis after re-irradiation in recurrent nasopharyngeal carcinoma

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With the development of radiotherapy technology and comprehensive treatment with chemotherapy, great progress has been made in the treatment of nasopharyngeal carcinoma (NPC) [1]. Unfortunately, some patients still suffer from local recurrence, the main treatment for which is still radiotherapy [2–4]. Although the incidence of massive epistaxis after re-irradiation is not high [5], it is a challenging situation that clinicians have to face because improper treatment may lead to death. This article reports one case of recurrent attacks of massive epistaxis after radiotherapy for locally recurrent NPC.

A 50-year-old man, diagnosed in August 2006 with low-differentiated NPC T2N2M0 (according to the Chinese 1992 staging system [6]), underwent three-dimensional conformal radiotherapy at a total dose of 70 Gy/35 fx and received concurrent and adjuvant chemotherapy (using the cisplatin-fluorouracil, also known as the PF, regimen). After five cycles of chemotherapy, evaluation of treatment response demonstrated complete regression. Regular magnetic resonance imaging (MRI) follow-up was provided. The patient came to our hospital again in February 2011 because of tongue movement impairment, which was diagnosed as a local recurrence in the right parapharyngeal tissue by MRI and positron emission tomography (PET)-computed tomography (CT) examination (Fig. 1). Intensity-modulated radiation therapy with a total dose of 70 Gy/35 fx was applied to the recurrent lesion, during and after which the patient again received four cycles of chemotherapy (using the paclitaxel-cisplatin, also known as the TP, regimen).

The patient was admitted to hospital for the third time in June 2011 because of headache and right facial pain and swelling, with an odorous exhalation from the nose and mouth. The nasopharyngeal MRI examination showed a necrotic change in the right parapharyngeal tissue, with inclusion of the internal jugular artery and vein, the external jugular artery and vein, and the lingual artery and vein. The necrotic tissue extended from the nasopharynx to the oropharynx (Fig. 2). After examination, it was considered septic abscess formation surrounding the right carotid sheath due to ulceration and necrosis of the nasopharyngeal mucus after re-irradiation. Thus, antibiotics and cortisol were given.

The patient presented with epistaxis of about 20 ml on the second day of hospitalization, which ceased spontaneously without special treatment. No bleeding site was seen by clinical examination of the oropharynx and nasopharynx, except for necrotic tissues at the site of the right nasopharynx.

The patient had hemorrhage through the nasal and oral cavities of about 300 ml on the third day. Through physical examination, the bleeding site was found at the lateral wall of the right nasopharynx close to the choanae, and by gauze packing at this site, satisfactory hemostasis was temporarily achieved. Unfortunately, epistaxis 200 ml in volume at the same site recurred 10 h later, and it was stopped by changing the gauze packing. The packing was removed 2 days later, and no further epistaxis occurred. We believe that the epistaxis was due to hypervascularization in the parapharyngeal tissue and diabrosis of the vascular wall, for which anti-inflammatory agents and other symptomatic care were further administered.

On the 17th day of hospitalization, he again presented with over 100 ml of hemorrhage in the oral cavity that could not be stopped by a choanal balloon tamponade. This epistaxis lasted for about 3 min before it stopped on its own. Large amounts of blood effused from the nose and the mouth 1 h later, and because the maximal inter-incisor distance was only about 1.5 cm, localizing the bleeding was difficult. Based on the previous MRI, we managed to stop the bleeding by compression on the right lateral wall of the nasopharynx using sterile gauze wrapped around the right index finger. No active hemorrhage was observed after 30 min of sustained pressure. The total amount of bleeding was about 1000 ml. The hemorrhage led to a hypotensive state that was corrected with fluid resuscitation and blood transfusion. Head and neck surgeons were consulted, and they all deemed the patient unsuitable for carotid artery ligation surgery because of neck fibrosis and the existing local infection.

A digital subtraction angiography (DSA) examination was done immediately after bleeding was stopped, but minimal oral hemorrhage of about 50 ml reappeared during DSA. The angiography showed pseudoaneurysm formation at the right lingual artery with contrast agent leakage. Stent placement was not suitable because of
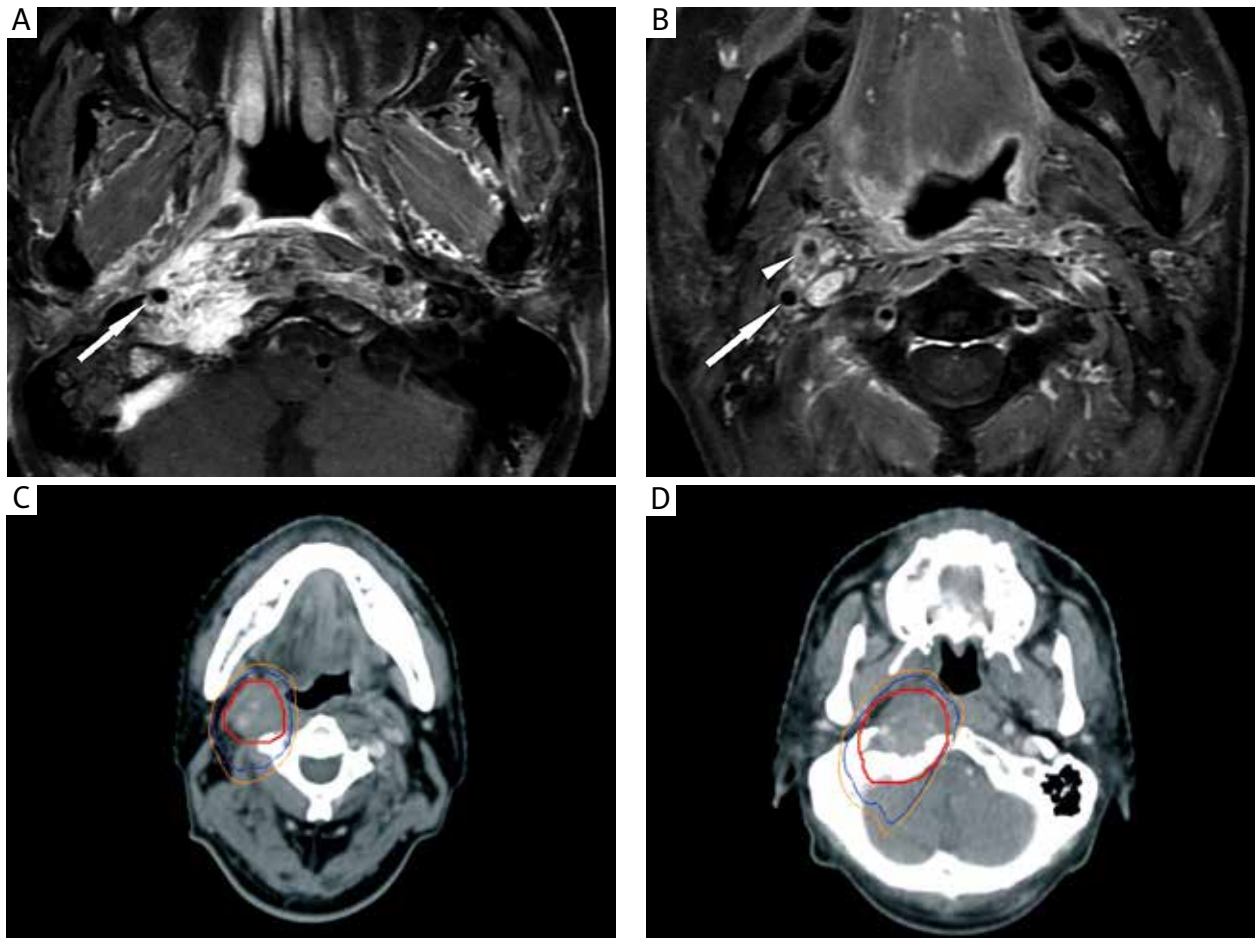
Fig. 1. A) Irregular mass located on posterolateral side of right pharyngeal region was seen as hyperintense in MRI-T1WI before re-irradiation, involving the right pre- and paravertebral muscles and dura mater. Arrow indicates the mass surrounding the internal carotid artery. **B)** Level of branching of lingual artery from external carotid artery: Heterogeneous signal in tissue around the lingual artery (arrow head), the obvious intensified mass after enhancement was seen on the posteromedial side. The internal carotid artery is located posterolaterally (arrow). **C)** The lingual artery level dosage distribution curve. Red line: Gross tumor volume (GTV). Yellow line: 100% isodosage curve. Blue line: 95% isodosage curve. The lingual artery and the internal carotid artery received a dose no less than 100%. **D)** Dosage distribution curve on the mastoid process level: the intracranial segment of the internal carotid artery is surrounded by the tumor

the buckling of the lingual artery and its small diameter. Moreover, the pseudoaneurysm body was too close to the openings of the lingual artery. Therefore, we decided to perform detachable coil embolization instead. The coils were placed in the starting segment of the right lingual artery. Postoperative angiography showed that the coils were predominantly in the right lingual artery, part of which was backed into the external carotid artery, and the lingual artery was not visualized (Fig. 3). Bleeding no longer occurred after the interventional therapy, and the anti-inflammatory treatment was continued. The follow-up CT showed an evacuation of the right parapharyngeal necrotic tissues. The CT angiography (CTA) showed a stenotic extracranial segment of the right internal carotid artery due to compression, and atherosclerotic plaque formation at the right common carotid artery bifurcation and the lower segment of the left common carotid artery was evident (Fig. 4). The right external carotid artery was not visible using CTA. Given the location of the right carotid artery in the necrotic tissue, a high possibility of the rupture, ligation, or embolization of the right carotid artery was

indicated. The patient was taught to press intermittently on the right carotid artery to establish adequate collateral circulation between the two hemispheres; otherwise, the patient could have had an ischemic necrosis of the right hemisphere due to the occlusion of the right carotid artery.

On the 43rd day, only episodes of minimal oral epistaxis, with a volume of about 5 ml per episode, were observed in the patient. These episodes ceased spontaneously.

Massive bleeding of about 500 ml in the oropharynx and nasopharynx recurred on the 44th day, and it was temporarily stopped by a nasal balloon tamponade. The CTA examination given on the same day revealed pseudoaneurysm formation at the extracranial part of the right internal carotid artery accompanied by fatty plaque formation. The resulting minimum diameter of the artery was only 2.4 mm, which is unsuitable for stent placement. The internal carotid artery balloon tamponade test given afterwards demonstrated the development of collateral circulations between the cerebral hemispheres, with adequate blood supply to the right hemisphere.
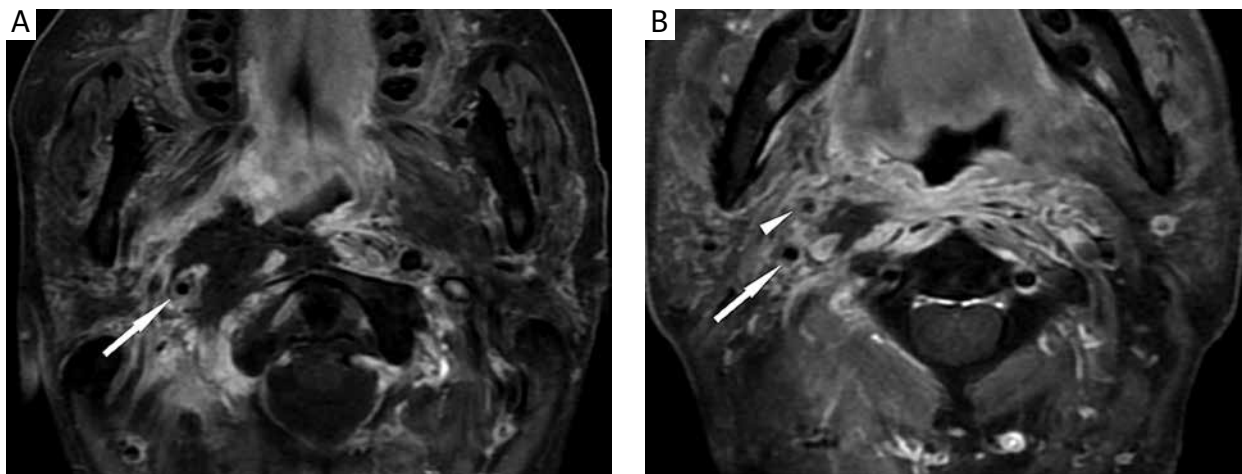
Fig. 2. A) MRI-T1WI before anti-inflammatory treatment: right parapharynx liquefied necrotic area surrounding the right internal carotid artery sheath. **B)** Lingual artery level: liquefied necrotic tissue can still be seen in the parapharyngeal space

Upon obtaining consent from the patient and his family, coils were placed in the pseudoaneurysm and also at a position 12 cm distal to the tumor body to prevent blood reflux. The postoperative angiogram could not provide an image of the right internal and external carotid arteries but showed that there was ideal blood supply to the right hemisphere (Fig. 5). A total of 8 units of red blood cells were transfused during hospitalization. Epistaxis has not recurred for two months since the last episode. Except for limited mouth opening, no symptoms of ischemia have developed. The patient has continued to receive anti-inflammatory treatment.

Although great progress has been gained in the diagnosis and treatment of NPC, local recurrence, which requires re-irradiation, is frequently observed. Massive epistaxis after re-irradiation, despite its low incidence, is one of the most challenging situations in clinical practice.

No cases have been reported on several attacks of massive epistaxis after radiotherapy. In this article, we report a case of successful treatment of repeated massive epistaxis after re-irradiation for NPC.

Epistaxis after radiotherapy of NPC is relevant to various factors [5, 7]. The direct infiltration of the tumor into vessel walls, the deposition of subintimal fibrous-like substances, the degeneration and decreased elasticity of the medial muscle fiber, the fibrosis of adventitia, and the foam cell aggregation in vessel walls are all contributing factors to the fragility of vessels after radiotherapy; thus, the smaller the vessels, the greater the damage is [8]. Accordingly, we divide local recurrence lesions into two types according to the incidence rate of massive epistaxis. The first type, with large vessels in the recurrence lesions, is very prone to epistaxis and is susceptible to subsequent local infection. It is mainly found in the local failure of the parapharyngeal space and basal skull. The other type, with a lower incidence rate, is a lesion supplied by microvessels with lower infection rates, such as a recurrence in the orbit and paranasal sinus.

To our knowledge, this patient with lingual artery hemorrhage in NPC is a new case. The right lingual artery of the patient was found in the recurrent lesion. After receiving re-irradiation, it became surrounded by areas of infection.

Fig. 3. DSA showed the right lingual artery pseudoaneurysm (arrow head), and the right internal carotid artery (arrow). Coils were placed at the opening of the right lingual artery and in the pseudoaneurysm, part of which retreated into the internal carotid artery. DSA was repeated after spring coil placement, which showed good development of the right internal carotid artery with delayed development of the external carotid artery and non-development of the lingual artery
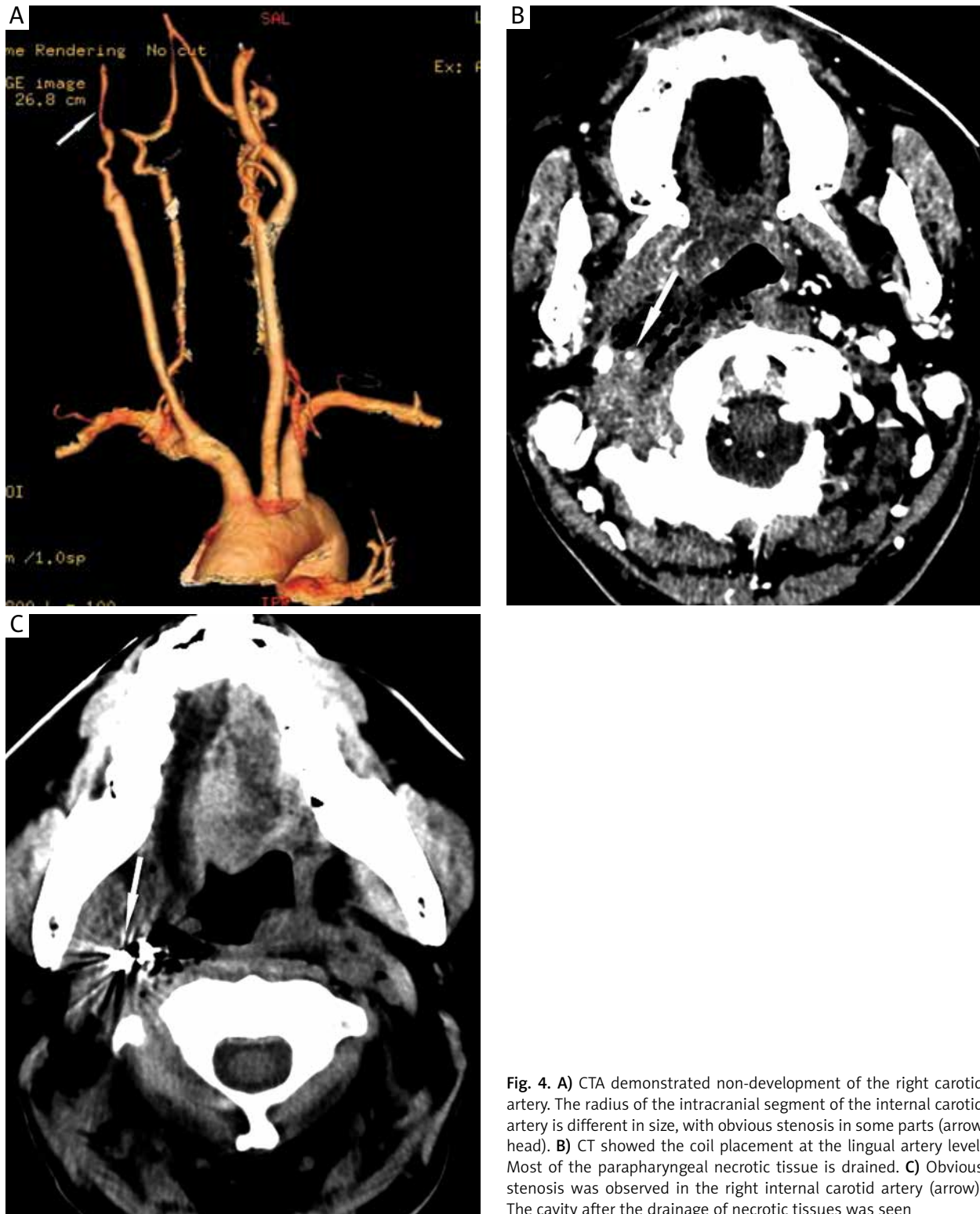
Fig. 4. A) CTA demonstrated non-development of the right carotid artery. The radius of the intracranial segment of the internal carotid artery is different in size, with obvious stenosis in some parts (arrow head). **B)** CT showed the coil placement at the lingual artery level. Most of the parapharyngeal necrotic tissue is drained. **C)** Obvious stenosis was observed in the right internal carotid artery (arrow). The cavity after the drainage of necrotic tissues was seen

Finally, it developed a pseudoaneurysm and ruptured. Compared with the trunk of the internal and external carotid arteries, the small branches of the lingual artery, with their thinner walls, are more prone to rupture. Moreover, because of injuries from radiotherapy and infection, the healing of these branches by themselves is difficult. Therefore, these small branches that receive very high doses of radiotherapy

within the foci of the infection are regarded as high-risk vessels, to which intensive attention should be given. Where there are high-risk vessels in the massive epistaxis area, the DSA or CTA examinations should be completed as soon as possible to achieve a prompt diagnosis.

Rupture and bleeding of pseudoaneurysms are not rare in previous reports [5, 7, 9]. Head and neck hemorrhage

Fig. 5. A) DSA showed the right internal artery with different diameters, arrow head: the pseudoaneurysm. **B)** Balloon tamponade test demonstrated a good right hemispherical blood supply; **C)** Arrow shows the coil in the internal carotid artery. Second imaging after coil placement, right internal carotid artery was not developed

has been called the "carotid blowout syndrome" [10] by some clinicians for its complexity and aggressiveness. Early awareness of the warning signs of massive bleeding may help improve the survival rate of patients.

Massive epistaxis in this patient came after episodes of small amounts of bleeding (less than 100 ml) in the nasal or oral cavity, and it stopped shortly thereafter on its own. This problem is one that clinicians tend to underestimate because in more than a few hours, uncontrollable massive epistaxis amounting to approximately hundreds of milliliters could become a great problem.

According to the examination of this patient, the small amounts of bleeding might have been caused by the rupture of small vessels that were stopped by thrombosis. The epistaxis became uncontrollable when the thrombus dissolved, and thus vessel injuries increased, and the ruptures enlarged because of the focus of the nearby chronic infection. Therefore, a small amount of epistaxis can serve as a warning sign of massive epistaxis, demanding the thorough consideration of the causes of the epistaxis and the preparation of emergency measures aside from the enhanced anti-infection treatment for patients with a high risk of massive epistaxis.

Treatments for head and neck massive epistaxis include direct compression, ligation of the cervical blood vessels, and interventional therapy, among others. The ligation of the cervical vessels is not the treatment of choice for patients with massive epistaxis after radiotherapy of nasopharyngeal carcinoma because of the fibrosis of the cervical skin and the focal infection after irradiation, which may hinder any operation and the healing process after surgery [11, 12].

For relatively superficial, visible active hemorrhagic focus, compression may quickly stop the bleeding. However, for vessels that are found deep in the tissue, compression is impossible, and hemorrhage from them may be lethal. With the progress in interventional techniques, more patients are now able to receive intravascular interventional treatments, such as the use of coated stents, permanent balloon occlusion, Guglielmi detachable coil (GDC) embolization, and the administration of thrombotic drugs, each with its own respective merits [13–15, 17, 18]. The most common side effects are in the form of ischemic changes,

such as a stroke, especially after the complete embolism of the ipsilateral carotid trunk.

In this case, because of their tortuous vessel course and the limitations of their intraluminal diameter, the lingual artery and internal carotid artery pseudoaneurysms were both treated by detachable coil embolization, which proved to have an adequate hemostatic effect. Concerning the probability of the rupture of the right carotid artery, this patient was taught to practice intermittent right carotid artery compression for three weeks, which established the ideal collateral circulation in the right hemisphere, as confirmed by DSA. The patient was spared from the adverse effects of intracranial hemorrhage after the transcatheter embolism of the internal carotid artery.

We recommend this adaptive compression exercise as a preventive technique in future clinical practice. The exercise should be performed before embolization so that it may establish collateral circulation in advance to minimize the side effects caused by the embolism.

Apart from the timely hemostatic treatments, the proper control of infections also plays a crucial role in the prevention of recurrent hemorrhage. The vessel injuries remain unrepaired or worsen while they are surrounded by a sustained infection focus. The odds of parapharyngeal necrosis greatly increase after re-irradiation, and its pathogenesis remains obscure, although the limited collagen synthesis, the lowered cell division capacity, and the deactivated tissue degradation and healing in the radiation field may partly explain this situation [16]. The management of necrotic parapharyngeal infections may be complicated and often long-lasting, requiring timely antibiotic adjustment and nasopharyngeal debridement when needed.

This paper reports a successfully treated case of repeated massive hemorrhage after radiotherapy of recurrent NPC with endovascular coil embolization. Different causes can lead to each instance of hemorrhage, even in the same patient. Thus, CTA and DSA play an important role in identifying the various causes. The probability of nasopharyngeal hemorrhage after re-irradiation is higher in tumor beds with large embedded vessels, especially in areas susceptible to infection. The so-called high-risk vessels, which receive very high doses of radiotherapy and are located in the infection focus, should receive close clinical attention. Minimal nasopharyngeal hemorrhage may serve as

a warning sign of massive epistaxis in high-risk patients. Thus, preparation for emergency measures is required, with endovascular coil embolization as the primary means of treatment.

Summary

1. Past studies show that massive epistaxis after re-irradiation in recurrent NPC is one of the most challenging situations that clinicians face.
2. Early prediction and prompt treatment are the key steps to reduce the risk of death during massive epistaxis.
3. We reported a case of successful treatment of recurrent attacks of massive epistaxis after radiotherapy in recurrent NPC using endovascular methods.
4. The results show that embolization with an endovascular coil achieved excellent hemostasis.
5. We posit that minimal hemorrhage in high-risk patients may be a warning sign of massive epistaxis, and thus emergency measures should be prepared immediately, with endovascular methods as the primary means of treatment.

References

1. Lu H, Peng L, Yuan X, et al. Concurrent chemoradiotherapy in locally advanced nasopharyngeal carcinoma: A treatment paradigm also applicable to patients in Southeast Asia. Cancer Treat Rev 2009; 35: 345-53.
2. Chang JT, See LC, Liao CT, et al. Locally recurrent nasopharyngeal carcinoma. Radiother Oncol 2000; 54: 135-42.
3. Poon D, Yap SP, Wong ZW, et al. Concurrent chemoradiotherapy in locoregionally recurrent nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2004; 59: 1312-8.
4. Chua DT, Sham JS, Leung LH, Au GK. Re-irradiation of nasopharyngeal carcinoma with intensity-modulated radiotherapy. Radiother Oncol 2005; 77: 290-4.
5. Wong GK, Chan KK, Yu SC, Tsang RK, Poon WS. Treatment of profuse epistaxis in patients irradiated for nasopharngeal carcinoma. ANZ J Surg 2007; 77: 270-4.
6. Min H, Hong M, Ma J, et al. A new staging system for nasopharyngeal carcinoma in China. Int J Radiat Oncol Biol Phys 1994; 30: 1037-42.
7. Low YM, Goh YH. Endovascular treatment of epistaxis in patients irradiated for nasopharyngeal carcinoma. Clin Otolaryngol Allied Sci 2003; 28: 244-7.
8. Jurado JA, Bashir R, Burket MW. Radiation-Induced Peripheral Artery Disease. Catheter Cardiovasc Interv 2008; 72: 563-8.
9. Cheng KM, Chan CM, Cheung YL, Chiu HM, Tang KW, Law CK. Endovascular treament of radiation-induced petrous internal carotid artery aneurysm presening with acute haemorrhage. A report of two cases. Acta Neurochir (Wien) 2001; 143: 351-5.
10. Borsany SJ. Rupture of the carotids following radical neck surgery in irradiated patients. Ear Nose Thtort J 1962; 41: 531-3.
11. Cohen J, Rad I. Contemporary management of carotid blowout. Curr Opin Otolaryngol Head Neck Surg 2004; 12: 110-5.
12. Powitzky R, Vasan N, Krempl G, Medina J. Carotid blowout in patients with head and neck cancer. Ann Otol Rhinol Laryngol 2010; 119: 476-84.
13. Broomfield SJ, Bruce IA, Luff DA, Birzgalis AR, Ashleigh RJ. Endovascular management of carotid blowout syndrome. J Laryngol Otol 2006; 120: 694-7.
14. Chang FC, Lirng JF, Luo CB, Wang SJ, Wu HM, Guo WY, Teng MM, Chang CY. Patients with head and neck cancers and associated postirradiated carotid blowout syndrome: Endovascular therapeutic metfods and outcomes. J Vasc Surr 2008; 47: 936-45.
15. Wan WS, Lai V, Lau HY, Wong YC, Poon WL, Tan CB. Endovascular treatment paradigm of carotid blowout syndrome: Review of 8-years experience. Eur J Radiol 2013; 82: 95-9.
16. Hua YJ, Chen MY, Qian CN, Hong MH, Zhao C, Guo L, Guo X, Cao KJ. Postradiation nasopharyngeal necrosis in the patients with nasopharyngeal carcinoma. Head Neck 2009; 31: 807-12.
17. Mok JSW, Marshall JN, Chan M, van Hasselt CA. Percutaneous embolization to control intractable epistaxis in nasopharyngeal carcinoma. Head Neck 1999; 21: 211-6.
18. Sadri M, Midwinter K, Ahmed A, Parker A. Assessment of safety and efficacy of arterial embolisation in the management of intractable epistaxis. Eur Arch Otorhinolaryngol 2006; 263: 560-6.

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