

Medullary Hemorrhagic Infarction after Radiation for Nasopharyngeal Carcinoma

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Abstract

Head and neck irradiation may lead to accelerated atherosclerosis over several years. Delayed stroke has been described after head and neck irradiation administered for a number of conditions. However, brain stem stroke has only rarely been associated with irradiation. We report a patient with medullary hemorrhagic infarction 6 years after radiotherapy for nasopharyngeal carcinoma. A 42-year-old normotensive Chinese male had rapid onset of vertigo, diplopia, ataxia, dysphagia, hypophonic dysarthria, hemiparesis, and respiratory distress. Cranial MR imaging 2 days after symptom onset showed medullary infarction, and cranial MR imaging 5 days after symptom onset showed medullary hemorrhage. He needed ventilatory support and died of bacterial pneumonia 1 month later. Other risk factors for stroke were absent. Hemorrhagic infarction in this patient was likely associated with the radiotherapy. Radiotherapy is the first choice of treatment for nasopharyngeal carcinoma, however, it may induce fatal medullary hemorrhagic infarction.

Key words: medullary hemorrhagic infarction, nasopharyngeal carcinoma, radiotherapy, radioencephalopathy, magnetic resonance imaging, diffusion weighted imaging

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Introduction

The incidence of nasopharyngeal carcinoma is more common among Chinese in southern China and Southeast Asia. The principal treatment for nasopharyngeal carcinoma is radiotherapy, even though it can cause late delayed neurological complications in 13% of treated patients, and can damage the brainstem and cervical cord in about 2% of patients (1-3). However, radiation-associated brain stem stroke has rarely been reported. Herein we report a Chinese man who had medullary hemorrhagic infarction 6 years after radiotherapy for nasopharyngeal carcinoma.

Case Report

A 42-year-old Chinese man was admitted for rapid onset of vertigo, diplopia, ataxia, dysphagia, hypophonic dysarthria, right hemiparesis and respiratory distress. Six years previously, the patient had been diagnosed as suffering from nasopharyngeal carcinoma. The histological finding was low differentiated squamous cell carcinoma. The patient received a radiation dose of 70 Gy in 7 weeks to the nasopharynx and adjacent structure, a further 60 Gy was administered to the soft tissue of the neck. The radiotherapy was delivered by linear accelerator (6 MV photon), once a day, five times per week. Bilateral opposing faciocervical fields to cover the nasopharynx and upper neck lymphatics in one volume, matched with one lower neck lymphatics were used (38 Gy/

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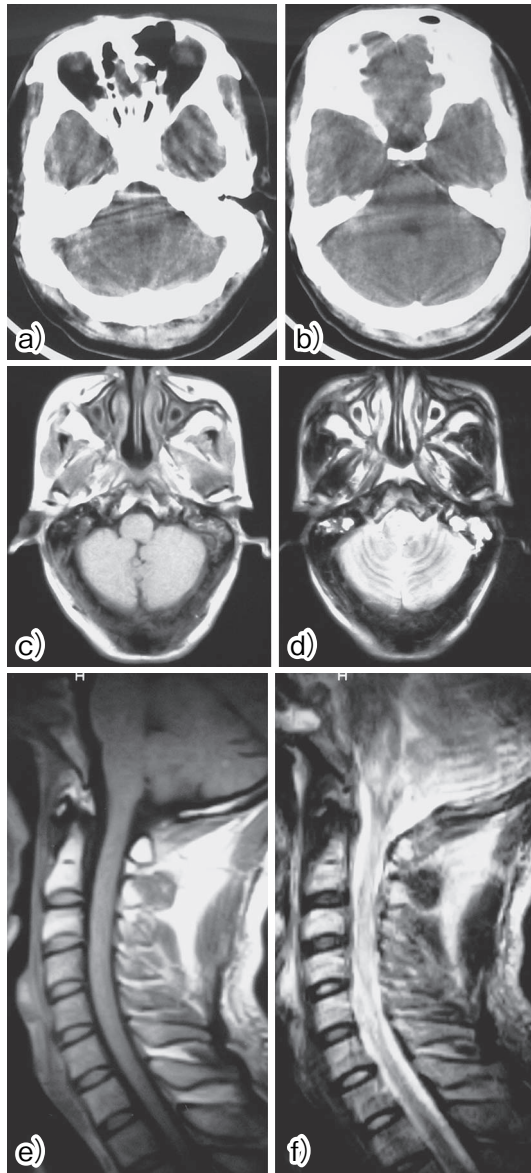


Figure 1. a) Cranial computed tomography on the first day of symptom onset showed no abnormality in the medulla oblongata, or b) in the pons. c) Cranial T1-weighted MR imaging 2 days after symptom onset showed no abnormality in the medulla oblongata, d) but T2-weighted imaging showed a lesion with hyperintensity in the medulla oblongata. e) Brain stem and cervical cord T1-weighted MR imaging 2 days after symptom onset showed no abnormality, whereas f) brain stem and cervical cord T2-weighted MR showed a lesion with hyperintensity in the medulla oblongata. [A movement artifact was present.]

19F/DT), then the split-field technique was used with two pre-auricular fields (22 Gy/11F/DT) and one pre-nasal field (10 Gy/5F/DT) for the nasopharynx, matched with an anterior cervical field for the neck lymphatics. The patient was treated with conventional radiotherapy, no dose volume histogram (DVH) was available at that time. Therefore, fields were reconstructed based on MRI data of this patient to get an idea of the dose distribution of brain stem. The anterior

margin of the brain stem received a dose of 60 Gy, while the center of the area where the hemorrhagic infarction did occur got a dose about 40 Gy. No neurotoxic radiosensitizer and no concurrent chemotherapy were used during radiotherapy. He was followed up every year and no clinical abnormality was found until he experienced bilateral progressive sensori-neural hearing loss 3 years previously (the left one was much more severe than the right). He had no history of stroke, coronary heart disease, arrhythmia, cardiomyopathy, hypertension, diabetes, peripheral atherosclerotic disease, nor any other disorders.

On admission he was afebrile, with blood pressure of 120/84 mmHg, heart rate of 84 beats per minute, and respiratory rate of 25 breaths per minute. He was alert, and had multidirectional crassitude nystagmus, a peripheral left facial palsy, dysarthria and dysphagia, bilateral hypoglossal palsy, right hemiparesis, right limbs hypesthesia, and dysmetria and dysdiadochokinesia of the bilateral limbs. The muscle strength of his right and left extremities was 4/5 and 5/5, respectively; the right plantar response was extensor and the left was flexor. His respiration was shallow.

Cranial computed tomography on the first day of symptom onset showed no abnormality (Fig. 1a, 1b). Cranial MR imaging 2 days after symptom onset in local hospital showed medullary infarction (Fig. 1c, 1d, 1e, 1f). Cranial MR imaging 5 and 7 days after symptom onset in our hospital showed a hemorrhagic lesion in the medullary region (Fig. 2a, 2b, 2c, 2d) and three small radio-encephalopathic lesions in the pons. The hemorrhagic lesion showed hyperintensity on T1-weighted MR imaging, heterogeneous intensity on T2-weighted MR imaging, diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping. Those radio-encephalopathic lesions showed hypointensity in T1-weighted MR imaging and showed hyperintensity in T2-weighted MR imaging, DWI and ADC mapping (Fig. 3a, 3b, 3c, 3d). All the lesions of the medulla and pons were not enhanced by gadolinium-diethylene triaminepentaacetic acid (Gd-DTPA) (Fig. 4a, 4b). Routine blood tests were normal. Cerebrospinal fluid was normal. Results of electrocardiogram, echocardiogram, ultrasonogram of abdominal organs, electroencephalogram, and transcranial Doppler were all normal. Nasopharyngeal endoscope showed that the mucosa of the nasopharynx was smooth, and there was no evidence of carcinoma recurrence. He was diagnosed with radiation-associated medullary hemorrhagic infarction and pontine radio-encephalopathy, and was treated with Tab prednisone (60 mg per day). He had not received any anti-coagulation or anti-platelet drugs.

One week after admission his breathing became more shallow, and he gradually lost consciousness. His breathing required assistance of a respirator. However, one month after the acute onset of the symptoms, he died of bacterial pneumonia.

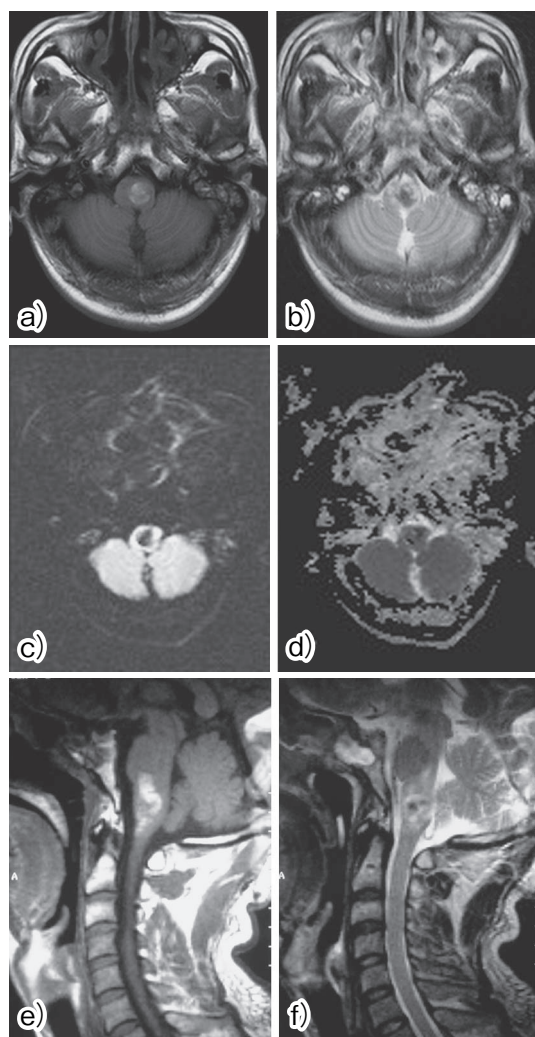


Figure 2. a) Cranial T1-weighted MR imaging 5 days after symptom onset showed a hemorrhagic lesion with hyperintensity in the medulla oblongata, and b) T2-weighted MR imaging showed a hemorrhagic lesion with heterogenous intensity in the medulla oblongata. c) Cranial diffusion-weighted imaging 5 days after symptom onset showed a medullary lesion with heterogenous intensity. d) Cranial apparent diffusion coefficient map 5 days after symptom onset showed a medullary lesion with heterogenous intensity. e) Brain stem and cervical cord T1-weighted MR imaging 7 days after symptom onset showed a hemorrhagic lesion with hyperintensity in the medulla oblongata and f) T2-weighted MR imaging showed a hemorrhagic lesion with heterogenous intensity in the medulla oblongata.

Discussion

Treatment of nasopharyngeal carcinoma is difficult because of the characteristic propensity of the tumour for extensive invasion and its anatomical proximity to critical structures. Although the optimum dose schedule has yet to be determined, it is agreed that doses below 60 Gy at conventional fractionation of 2 Gy daily are inadequate for tu-

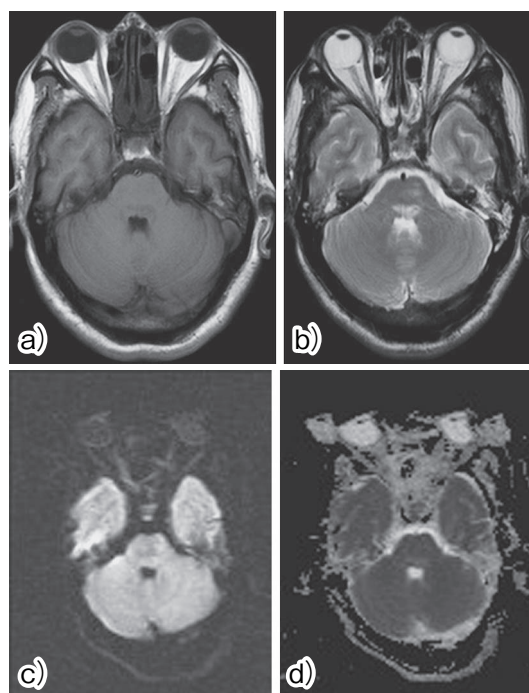


Figure 3. a) Cranial T1-weighted MR imaging 5 days after symptom onset showed a lesion with hypointensity in the dorsal pons, and b) T2-weighted MR imaging showed 3 pontine lesions with hyperintensity. c) Cranial diffusion-weighted imaging 5 days after symptom onset showed pontine lesions with hyperintensity at the corresponding sites to those lesions on T2-weighted MR imaging. d) Cranial apparent diffusion coefficient map 5 days after symptom onset showed pontine lesions with hyperintensity at the corresponding sites to those on T2-weighted MR imaging.

mor eradication. Thus, all normal tissues within the target volume will be exposed to a potentially damaging dose. Neural structures adjacent to the base of the skull, including temporal lobes and the brain stem, are particularly vulnerable (1-3). Radiation-induced brain stem encephalopathy and cervical spinal cord myelopathy are the most serious sequelae, the reported incidence ranges from 0.2% to 18%, with a median of 2% (1-3). However, brain stem stroke after radiation in nasopharyngeal carcinoma has rarely been reported.

Herein we report a case of fatal medullary hemorrhagic infarction 6 years after radiotherapy for nasopharyngeal carcinoma. He eventually died of respiratory distress and pulmonary infection. The first cranial MR imaging showed medullary infarction, and the second MR imaging 3 and 5 days after the first cranial MR imaging showed medullary hemorrhage in the same position. Therefore, the diagnosis of medullary hemorrhagic infarction was considered. Medullary hemorrhagic infarction in this patient was likely associated with radiotherapy for the following reasons: 1) The brain stem was located in the radiation field, there were radionecrotic lesions adjacent to the hematoma and the patient had left progressive sensori-neural hearing loss three years after radiotherapy, which implied the brain stem and cranial

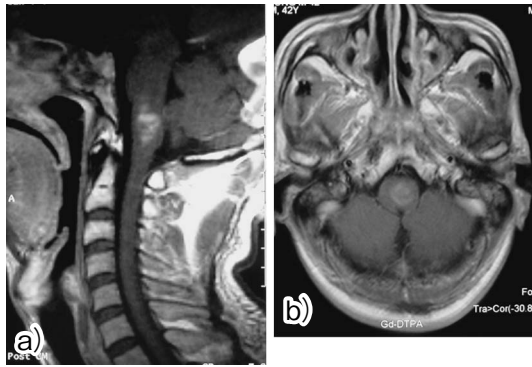


Figure 4. a) Sagittal brain stem and cervical cord enhanced T1-weighted MR imaging 7 days after symptom onset showed a medullary hemorrhagic lesion without enhancement. b) Axial cranial enhanced T1-weighted MR imaging 5 days after symptom onset showed a medullary hemorrhagic lesion without enhancement.

nerves had sustained irradiation injury. 2) The hemorrhagic infarction in this patient was not caused by vascular malformation because cerebral hemorrhagic infarction seldom happens in vascular malformation. Lack of any flow void in the medullary parenchyma did not support the existence of other kinds of vascular malformation, such as arteriovenous malformation, capillary malformations, and developmental venous anomaly. Cranial MR imaging of this patient did not show the distinct feature of cavernous malformation, i.e., a reticulated core of mixed signal intensity with a surrounding rim of decreased signal intensity representing hemosiderin from previous hemorrhaging. Lack of abnormalities in the cranial CT and the first cranial T1-weighted MR imaging in the medullary region further helped to exclude the diagnosis of cavernous malformation. 3) The patient had no clinical or pathological evidence of relapse of nasopharyngeal carcinoma. Cranial MR imaging also excluded the possibility of tumor-induced hemorrhagic infarction. 4) The patient did not have common risk factors or a family history of stroke.

Accelerated atherosclerosis is a well-recognized complication of irradiation (4, 5). An association between high-dose cervical irradiation for squamous cell carcinoma of the head

and neck and stroke has been demonstrated retrospectively by Haynes et al (6). Of their 413 patients, 20 had strokes occurring between 2 and 146 months after radiotherapy. The 5-year actuarial rate of stroke was 12%, which corresponded to a relative risk of 2.09 ($P=0.0007$) compared with the population-based “expected” data. Median radiation therapy dose was 64 Gy; there was no correlation between radiation therapy dose and stroke risk. Carotid artery stenosis is a late complication that is shown to be consistently related to radiotherapy for nasopharyngeal carcinoma (7, 8), however, vertebral artery stenosis or brain stem infarction induced by irradiation for nasopharyngeal carcinoma was rarely reported (9-11). Although conventional cerebral angiography or MR angiography was not done for the present patient, transcranial Doppler of our patient did not show any abnormality. Thus, there might not be any significant stenotic lesions in the carotid or vertebral arteries. From our experience, vertebral artery commonly compensates the severely stenotic carotid arteries induced by radiotherapy for nasopharyngeal carcinoma. Therefore, we presumed that the hemorrhagic infarction in the present patient was caused by irradiation-induced vasculopathy of the small arteries supplying the medulla oblongata.

Irradiation-induced stroke which is commonly ischemic, delayed cerebral hemorrhage or hemorrhagic infarction caused by irradiation has only rarely been reported (12-15). The present case was the first case to have medullary hemorrhagic infarction following irradiation for nasopharyngeal carcinoma. Irradiation-induced vasculopathy might have the potential to cause hemorrhage or hemorrhagic transformation. The hemorrhagic transformation was not induced by anti-coagulant or anti-platelet drugs, because the patient had not received such drugs. He did not have a history of heart disease or peripheral atherosclerotic artery disease, and there was no evidence to show that he had embolic infarction which had transformed to hemorrhagic infarction.

In conclusion, radiotherapy for nasopharyngeal carcinoma might induce fatal medullary hemorrhagic infarction. The brain stem is the key area to be protected during radiotherapy for these patients.

References

1. Lee AW, Law SC, Ng SH, et al. Retrospective analysis of nasopharyngeal carcinoma treated during 1976-1985: late complications following megavoltage irradiation. *Br J Radiol* **65**: 918-928, 1992.
2. Song T, Liang BL, Huang SQ, Xie BK, Ding ZX, Shen J. Magnetic resonance imaging manifestations of radiation injury in brain stem and cervical spinal cord of nasopharyngeal carcinoma patients after radiotherapy. *Ai Zhong* **24**: 357-361, 2005.
3. Chong VF, Khoo JB, Chan LL, Rumpel H. Neurological changes following radiation therapy for head and neck tumours. *Eur J Radiol* **44**: 120-129, 2002.
4. Comomy JP, Killermeyer RW. Delayed cerebrovascular consequences of therapeutic radiation. *Cancer* **6**: 1702-1708, 1975.
5. Cheng SW, Ting AC, Ho P, Wu LL. Accelerated progression of carotid stenosis in patients with previous external neck irradiation. *J Vasc Surg* **39**: 409-415, 2004.
6. Haynes JC, Machtay M, Weber RS, Weinstein GS, Chalian AA, Rosenthal DI. Relative risk of stroke in head and neck carcinoma patients treated with external cervical irradiation. *Laryngoscope* **112**: 1883-1887, 2002.
7. Lam WW, Yuen HY, Wong KS, Leung SF, Liu KH, Metreweli C. Clinically underdetected asymptomatic and symptomatic carotid stenosis as a late complication of radiotherapy in Chinese nasopharyngeal carcinoma patients. *Head Neck* **23**: 780-784, 2001.
8. Cheng SW, Ting AC, Lam LK, Wei WI. Carotid stenosis after radiotherapy for nasopharyngeal carcinoma. *Arch Otolaryngol Head Neck Surg* **126**: 517-521, 2000.
9. Miyahara K, Suzuki S, Gondo G, Kanno H, Yamamoto I. Surgical

- reconstruction for radiation-induced extracranial vertebral artery stenosis: a case report. *No Shinkei Geka* **29**: 985-990, 2001 (in Japanese).
10. Steiner H, Hackl A, Lammer J. Radiation-induced vasculopathy of the carotid artery and vertebral artery. *Rontgenblätter* **37**: 320-321, 1984 (in German).
 11. Graef LM, Lutsep HL, Norbash A, Albers GW. Use of fluid attenuating inversion recovery, MR angiogram, and diffusion-weighted MRI techniques for assessment of pontine infarction in a patient treated with radiation therapy for pituitary neoplasm. *Neurology* **48**: 540-542, 1997.
 12. Lee JK, Chelvarajah R, King A, David KM. Rare presentations of delayed radiation injury: a lobar hematoma and a cystic space-occupying lesion appearing more than 15 years after cranial radiotherapy: report of two cases. *Neurosurgery* **54**: 1010-1013, 2004.
 13. Hillemanns A, Kortmann RD, Herrlinger U, Skalej M, Krapf H. Recurrent delayed brain hemorrhage over years after irradiation and chemotherapy for astrocytoma. *Eur Radiol* **13**: 1891-1894, 2003.
 14. Azzarelli B, Moore J, Gilmor R, Muller J, Edwards M, Mealey J. Multiple fusiform intracranial aneurysms following curative radiation therapy for suprasellar germinoma. Case report. *J Neurosurg* **61**: 1141-1145, 1984.
 15. Ogaki S, Suzuki S, Suzuki H, et al. Cerebral hemorrhagic infarction after radiation for pituitary adenoma. *Intern Med* **41**: 834-838, 2002.