Malignant Astrocytoma Following Radiation for Nasopharyngeal Carcinoma: Case Report and Review of the Literature

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Abstract- A 32-year-old woman developed malignant astrocytoma 3 years after radiotherapy for nasopharnygeal carcinoma (NPC). Introduction of brain malignancy induction after external beam radiation for craniopharyngioma, pituitary adenoma, or meningioma has been previously reported. The theoretical risk of tumor induction in neural tissues, following radiotherapy by low-dose radiation has been verified, but the association of radiation-induced brain malignancy and NPC is extremely rare. We supposed that radiation exposure might play a promoter role in this immune-compromised patient who was previously at high risk of developing co-morbidity. We believe that the incidence of radiation-induced malignancies will increase in the future, and this warrants closer observation by physicians.

Key Words: Radiation-induced brain malignancy, Nasopharyngeal carcinoma

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INTRODUCTION

Conventional radiotherapy for nasopharyngeal carcinoma (NPC) delivered a high dose of radiation to the head and neck mass, particularly when the lesion was invasive intracranially[1,2]. It is difficult to spare the adjacent neural structures, even with good protection. The dosing effect of external beams cobalt-60, varying from 4000~7000 cGy totally to the target lesion in the nasopharynx, can lead to radiation injury, such as mucositis, swallow difficulty, xerostomia, hearing loss, or even temporal lobe necrosis[3-9], but the induction of a brain malignancy has been rarely reported. We report an immune-compromised patient who developed malignant astrocytoma 3 years after large dosing and wide-field irradiation to NPC with adjacent extension cranially, and this radiotherapy was considered to be a co-factor in this tumor growth. We also reviewed the literature regarding radiation injury with treatment for NPC and its associated morbidity.

CASE REPORT

A 32-year-old right-handed woman presented with mild right limbs weakness after a sentinel upper tract infection of sore throat and cough for 3 weeks in

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October 2003. She was rather smooth in past years according to the chart records. No hypertension or diabetic mellitus was noted. In July 2000, she received 5-FU plus Leucoverin for 10 weeks with concomitant a total radiation dose of 6300cGy for treatment of pathological-proven NPC (squamous cell carcinoma, stage III in T3M0N0), which invaded the right sphenoid sinus and was shown on the computed tomography (Fig. 1). No recurrence was found at follow-ups. She visited our neurological clinic due to muscle strength decline for 2 days. The neurological evaluation revealed no optic, eye movement, nor cerebellar lesions, but right limbs weakness and a Babinski's sign were elicited (muscle grading 4 on the upper limb, and 3 on the lower limb according to the Medical Research Council of Great Britain). Brain magnetic resonance imaging (MRI) in Oct. 2003 showed a left peri-trigone white matter lesion (Fig. 2). She received steroid therapy (hydro-cortisone 4mg intravenously every 6 hours) for 3 days successively under the impression of a demyelinating disease, such as acute disseminating encephalomyelitis (ADEM). The patient responded well and recovered her strength of the right extremities to nearly normal (grading 5 on the upper limb, and 4+ on the lower limb). In December 2003, relapse and progression of the right hemiplegia (grading 3 on the upper and lower limbs), associated with limb spasm were noted. A follow-up Gadoninium (Gd+) MRI in Dec. 2003 revealed an intervallic patch lesion without obvious enhancement (Fig. 3). Multiple sclerosis and progressive multifocal leukoencephalopathy were sus-

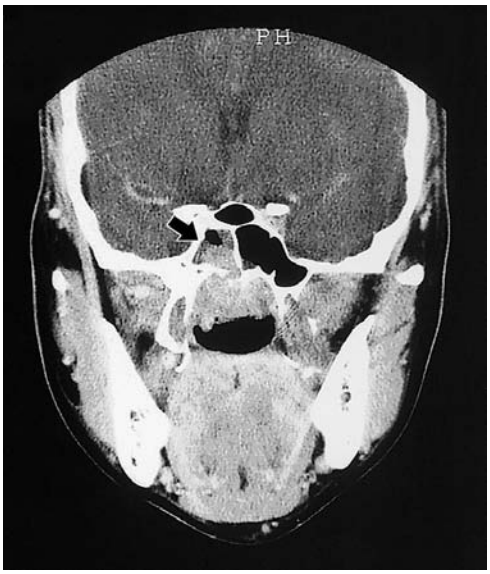

Figure 1. A nasopharyngeal soft tissue mass with invasion to the right sphenoid sinus (arrow).

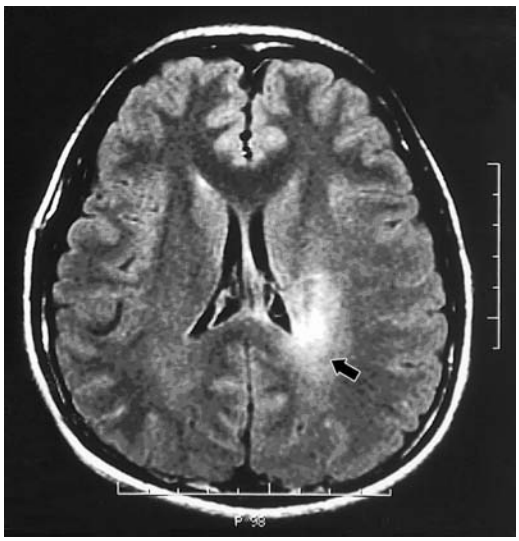

Figure 2. A peri-trigone white matter lesion on the flare image (arrow).

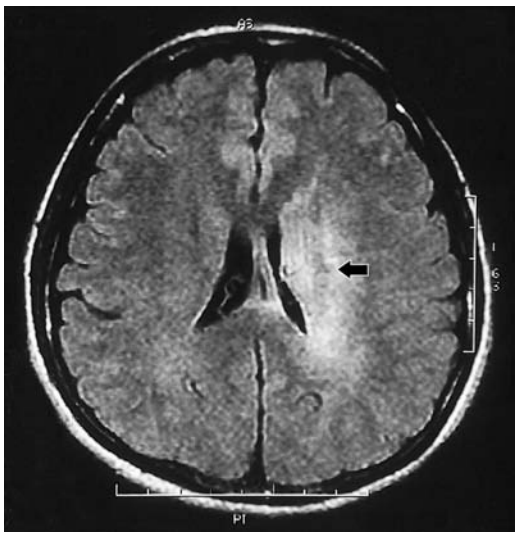

Figure 3. Gadoninium (Gd+) on T1-weighted image (T1W1) showing a mild extending lesion without strong enhancement demonstrated a demyelination process rather than a tumor-like mass (arrow).

pected. Normal cerebral spinal fluid, thyroid function, anti-double strain DNA, and peripheral leukocyte counts, but a low C3 level (77.8 ng/dl； normal limit: 90-180 ng/dl) and a low CD4/CD8 ratio (0.8; normal limit: 1.2-2.0) were noted. She received an advanced treatment with plasma exchange 1000c.c/day for 3 days, followed by an immunoglobulin (IVIg) (0.4 gm/kg/day) injection for another 3 days. The patient felt a remission of spastic limbs and improvement of muscle strength

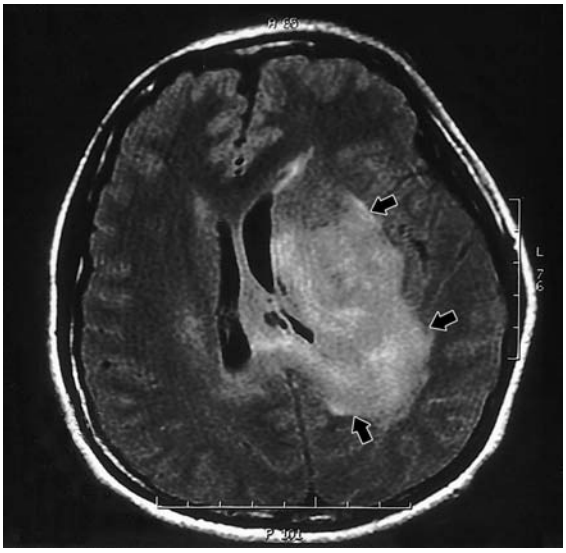

Figure 4. Transcallosal extension of a huge mass with a midline shift 5 months after the onset (arrows).

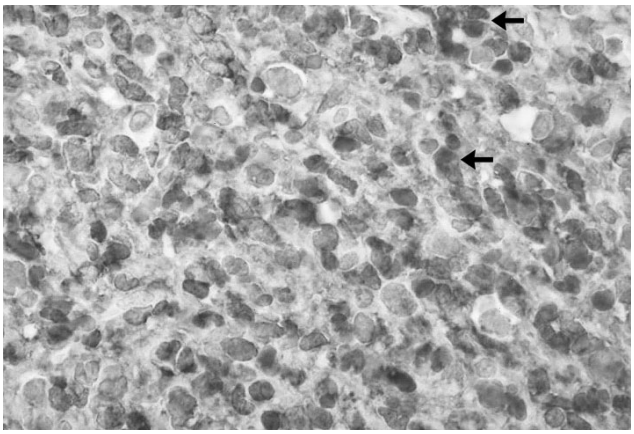

Figure 5. Pathology of dark nuclei, high cellulaity of astrocytes (arrows), on glial fibrillary acidic protein (GAFP) stains (400×).

(grading 4 on the upper, and 4+ on the lower limbs). After discharge, she continued rehabilitation for muscle strength, and received herbs drugs and prednisolone (20mg) once daily, with maintained a stable condition during the outpatient follow-up. Unfortunately, she was brought to emergency room in March 2004 in a stuporous state. High fever with urosepsis was noted, and she was transferred to an intensive care unit. The third MRI in Mar. 2004 revealed a trans-callosal extension of the mass lesion with a midline shifting (Fig. 4). A stereotactic biopsy revealed a high-grade astrocytoma (Fig. 5). She received a palliative treatment temporarily and was readied for radiotherapy. However, the patients' condition deteriorated, and recurrent sepsis with pancytopenia was noted. She died of septicemia and lung empyema. The diagnosis of septic shock and brain tumor in this immune-compromised patient, and co-existence of a presumed radiation injury, were the causes of death.

DISCUSSION

Radiation-induced brain malignancy including glioblastoma, sarcoma and carcinoma of the tongue has been documented[1,2]. Malignancy developing within the radiation field can be radiation-induced or coincidental. The most common adverse NPC irradiation effects were edema of mucosa, mucositis, difficulty swallowing, fatigue, tiredness, xerostomia, trismus, carotid stenosis, and pharyngeal stricture[3-7]. Radiation-induced brain encephalomalacia and temporal lobe necrosis have been reported, but the development of brain tumor was extremely rare[8,9]. In the study from Queen Mary Hospital in Hong Kong[10], 15 of 759 patients with NPC had secondary malignancy, but only 1 was related to the radiotherapy for NPC. In another report[2], radiation-induced sarcomas of the head and neck, due to radiotherapy for NPC, were demonstrated in 4 patients, of which 3 exposed a high radiation dosage had a tumor mass of 3.5cm or larger. Interestingly, 2 NPC cases developed glioblastoma and parotid myxoma 3 and 7 years after radiotherapy respectively[1].

The criteria for radiation-induced neoplasms were established by Cahan et al.[11], and were modified by

Schrantz et al.[12], as follows: 1) the tumor must appear in the irradiated area, 2) the tumor is not present prior to irradiation, 3) a sufficient latency period must elapse between irradiation and the appearance of the tumor, and 4) the radiation-induced tumor must be histologically proven and must be of a different type from the original tumor first treated with radiation therapy. Our case meets each of these above criteria, because the malignant astrocytoma occurred within the radiation field, 3 years after radiotherapy and pathological proven astrocytoma.

Adult cancer survivors have an increased risk of developing secondary malignant neoplasms[13], a well-recognized complication, especially in patients with Hodgkin's disease or non-Hodgkin's lymphoma treated with irradiation or combined chemotherapy[14]. The increased risk of secondary cancer can be attributed to the mutagenic risk of irradiation as well as immunosuppressive drugs[15]. A review of the literature, revealed that coincidental tumors associated with NPC were very rare, and were prove to occur in younger people[16]. In our patient, we are not sure that radiation is the only factor to this secondary glioma, because an immune or genetic origin, may play a part in this event. Therefore, patients undergoing radiation therapy should have a long-term follow-up for probable secondary malignancy beyond the primary cancer.

Brain malignancy induction after radiotherapy has been noted after radiation treatment with doses ranging from 400 to 6000 cGy, and an average latency period of 3-10 years for leukemia, pituitary adenoma, craniopharyngioma, or meningioma[17-19]. The risk of brain malignancy induction was higher than that in any part of the body after intracranial irradiation, but the mechanism was obscure[13,20]. With an incidence of brain tumors ranging from 5 to 10 per 100,000 people per year, the chance of occurrence of both tumors in one patient would be 1 in 1-5 billion[6,21]. Therefore, the random chance of both tumors in our patient would be very low. Given that the cranial margin of the tumor in this case received 20 Gy dose, the adjacent brain white matter would be expected to receive a dose of 5-10 Gy[21,22]. If the radiation dose accumulated to a critical level[23] (Table), the volume of the irradiated brain tissue would shrink in the beginning, another an abnormal mitosis might occur unexpectedly. From our imaging study, a huge tumor growth developed within half a year, a radiation-induced brain malignancy could be presumed based on the previous studies[24-26].

Table

Radiation		Probable Complication
Dose	Target	Endpoint
2-10 Gy	Lymphoid	Lymphopenia
	Testes	Sterility
	Ovocytes	Sterility
	Bone marrow	Leukopenia / Thrombopenia
10-20 Gy	Lens	Cataract
	Bone marrow	Acute apalasia
20-30 Gy	Kidney	Arterionephrosclerosis
	Lung	Pneumonitis
30-40 Gy	Liver	Hepatopathy/liver failure
40-50 Gy	Heart (whole organ)	Pericarditis
50-70 Gy	Gastrointestinal	Infarction necrosis
	Heart (partial organ)	Cardiomyopathy
	Spinal cord	Myelopathy
	Brain	Necrosis infarction
	Rectum	Ulcer
	Bones	Fracture
	Pancreas	Pancreatitis

1 Gy=100 cGy, Source from ref [23]

Radiation-induced gliomas occurred outside the field of radiotherapy and gliosis might predispose to brain tumor induction[27]. The dosages of radiation may play an important role in tumor rose of secondary malignancy with a lower dose inducing tumors <3cm in diameter, and with a higher dose >5000 cGy, inducing tumors >3cm[19]. From the low incidence of secondary malignancy, a high radiation dose, and the wide field of radiation the present case of secondary malignant astrocytoma was speculated to be radiation related or spontaneously brain cell mutation. It is still unknown how long the secondary tumor will develop after radiotherapy for NPC. In addition, radiation therapy to a head and neck mass warrants a close long-term follow-up for possible secondary malignancy.

CONCLUSION

Although the development of malignant astrocytoma

after radiotherapy for NPC treatment is very rare, it can occur, as in previous reports, based on the irradiating dose effect, the tumor size, the cranial invasion, and the host immune conditions. A co-incidental tumor growth can develop in an immune-compromised host, but it is extremely unusual, and there are few reports in literature of the co-morbidity of NPC with malignant astrocytoma. Attention should be paid to immune-compromised patients who have undergone radiotherapy, who had symptoms beyond primary lesions, who had a secondary tumor, or who had higher radiation dosages.

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