

# Spinal Cord Glioblastoma Induced by Radiation Therapy of Nasopharyngeal Rhabdomyosarcoma with MRI Findings: Case Report

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Radiation-induced spinal cord gliomas are extremely rare. Since the first case was reported in 1980, only six additional cases have been reported.; The radiation-induced gliomas were related to the treatment of Hodgkin's lymphoma, thyroid cancer, and medullomyoblastoma, and to multiple chest fluoroscopic examinations in pulmonary tuberculosis patient. We report a case of radiation-induced spinal cord glioblastoma developed in a 17-year-old girl after a 13-year latency period following radiotherapy for nasopharyngeal rhabdomyosarcoma. MRI findings of our case are described.

**Index terms:** Radiation induced glioma; Glioblastoma; Spinal cord; Rhabdomyosarcoma; Magnetic resonance imaging

## INTRODUCTION

Radiotherapy is an important therapeutic modality for the treatment of cancer, but has several reported side effects of radiotherapy. A radiation-induced neoplasm is a rare, but serious long-term complication. The majority of radiation-induced neoplasms of the central nervous system present as gliomas, meningiomas or sarcomas, and most are located intracranially (1). Secondary gliomas in the spinal cord after radiation therapy are extremely rare with, to the best of our knowledge, only seven cases reported in the literature (1-3). Four of these cases occurred after Hodgkin's disease treatment, and the other cases developed after multiple fluoroscopies and after radiotherapy for a thyroid carcinoma and medullomyoblastoma. Herein, we report a case of a

17-year-old girl with secondary spinal cord glioblastoma after radiotherapy for a nasopharyngeal rhabdomyosarcoma and describe magnetic resonance imaging (MRI) findings of radiation-induced spinal cord glioblastoma.

## CASE REPORT

A 17-year-old girl presented with a one-month history of numbness and hypesthesia of the left upper extremity in July, 2010. 13 years before the development of these symptoms, she had an embryonal nasopharyngeal rhabdomyosarcoma which was confirmed by excisional biopsy. She had undergone chemotherapy followed by radiotherapy. The radiotherapy consisted of a daily dose of 180 cGy and a total dose of 4500 cGy in 25 fractions. Radiation was delivered using right and left spinal ports, and the field of radiation covered the zygomatic area to the C6 level (Fig. 1A). In addition, she underwent two computed tomography (CT) scans and two simple radiographs of the cervical area at the time of rhabdomyosarcoma diagnosis of, and had additional six follow-up CT scans for six years until 2003. The CT scans, which were single-phase studies, had been performed using four different CT scanners with a kVp of 120 and a mAs ranging from 100 to 240. Radiologic and clinical follow-up revealed no evidence of recurrence

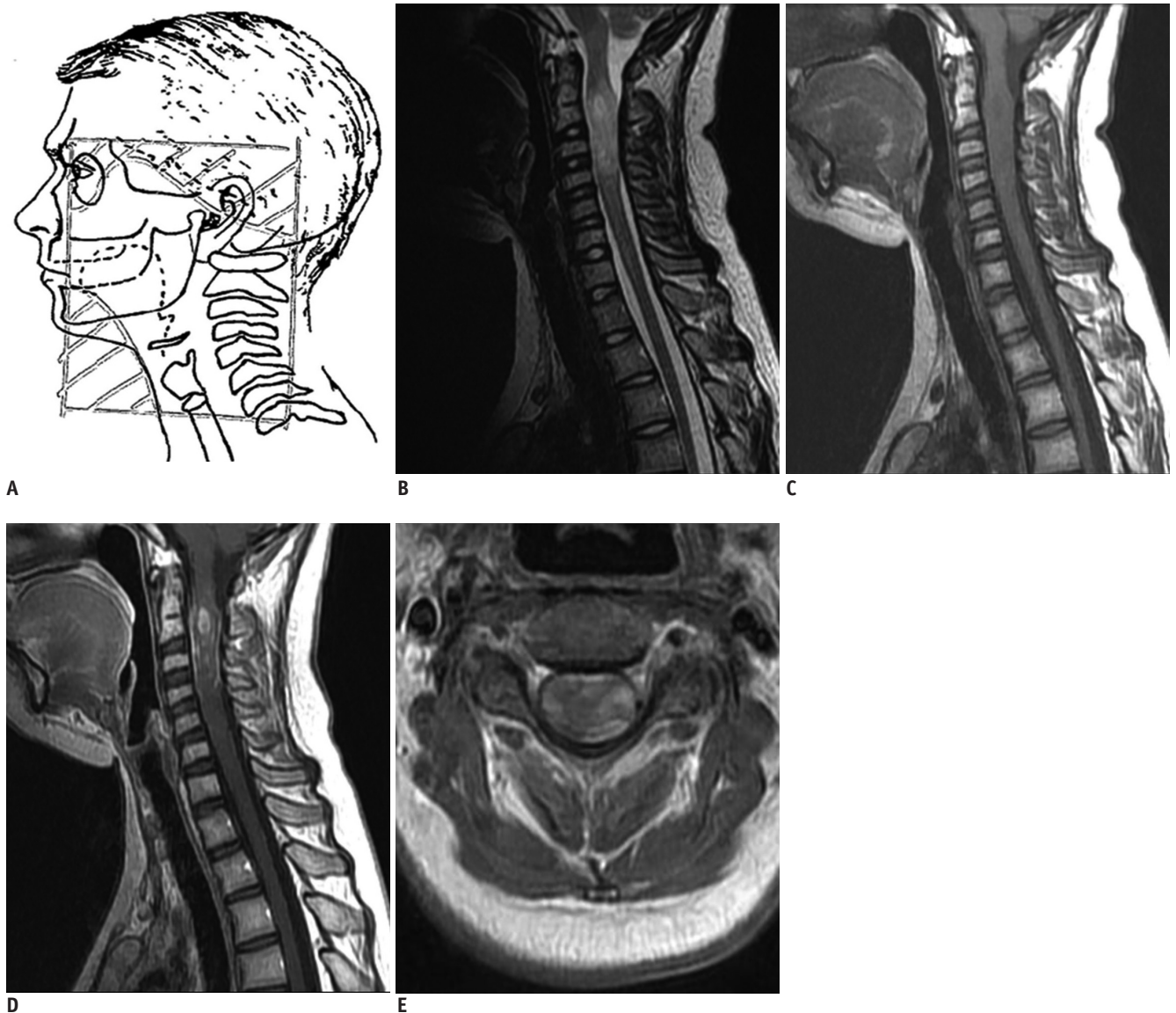
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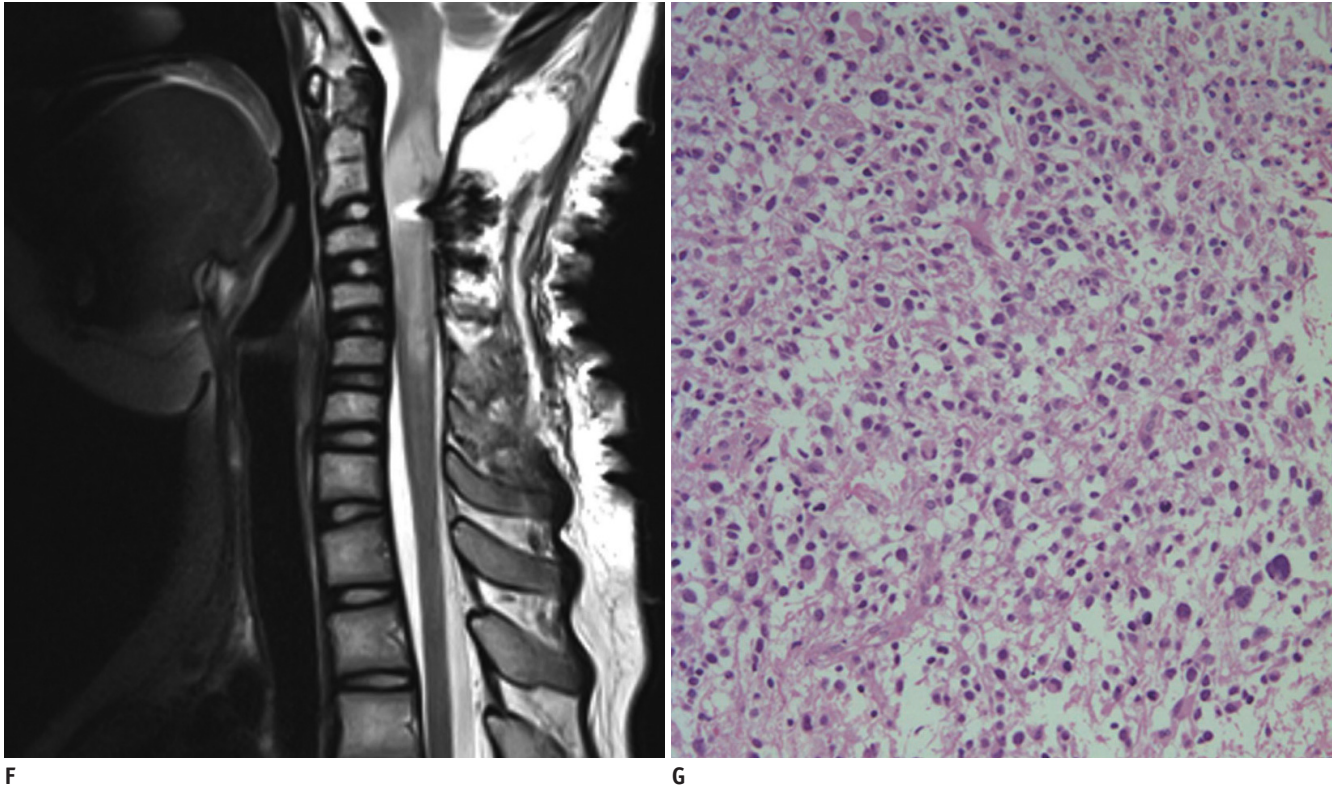
**Fig. 1. Magnetic resonance imaging and pathologic findings of radiation-induced spinal cord glioblastoma.**

**A.** Radiation field. Bidirectional right and left spinal ports were used and field of radiation coverage spanned zygomatic area to C6 level. Cervical spine MRI at symptom onset. **B.** Sagittal T2-weighted image shows diffuse enlargement and increased signal intensity of cervical cord from C2 to C4, which is accompanied with minimal edema. **C.** Sagittal T1-weighted image shows iso to hypo signal intensity compared to lesion. **D, E.** Contrast-enhanced sagittal (**D**) and axial (**E**) T1-weighted images show ring-like enhancement at periphery, nodular discrete enhancement at upper portion of lesion, and multiple stippled foci of enhancement.

through 2009. In July, 2010, she complained of newly appeared symptoms of numbness and hypesthesia of the left upper extremity. A physical examination revealed weakness of the left hand grasp and shoulder abduction as well as hypesthesia of the left upper extremity.

MRI of the cervical spine was performed (SIGNA EXICTE 1.5 T; GE Medical Systems, Milwaukee, WI, USA). We obtained both axial and sagittal T1-weighted images (T1WI) (TR 400 msec, TE 14.4 msec), T2-weighted images (T2WI) (TR 3716.7 msec, TE 118.6 msec), and post-contrast T1WI following intravenous injection of gadolinium-based

contrast agent (Magnevist; Bayer Schering Pharma AG, Germany). MRI showed a fatty change of bone marrow from the occiput to the cervical vertebra, corresponding to the previous field of radiation. T2WI demonstrated diffuse segmental enlargement of the cervical cord, from C2 to C4, measuring about 3.5 cm longitudinally, and resulting in the obliteration of the subarachnoid space. The lesion showed relatively homogeneous hyperintensity with minimal adjacent edema, and the margin of the lesion was poorly defined (Fig. 1B). T1WI revealed the tumor, which ranged from iso to hyposignal intensity (Fig. 1C). On post-contrast



**Fig. 1. Magnetic resonance imaging and pathologic findings of radiation-induced spinal cord glioblastoma.**

**F.** Cervical spine MRI on 11th postsurgical day: Residual mass has become more expanded, and longitudinal extent of abnormal high signal intensity increased on sagittal T2-weighted image. **G.** Photomicrography of glioblastoma shows neoplastic astrocytes with high cellularity, nuclear pleomorphism, and high frequency of atypical mitosis (H & E stain, magnifications x 200).

T1WI, an approximately 0.9 cm-sized nodular enhancement at the upper portion of the lesion and multiple stippled foci of enhancement were noted. In addition, peripheral rim of the involved segment was enhanced (Fig. 1D, E). MRI of the brain revealed no abnormal signal change or enhancement of the parenchyma.

The patient underwent a surgical biopsy, followed by a laminectomy from C2 through C4. The cervical cord was found to be diffusely enlarged, and the tumor was barely differentiable from normal tissue. Histological evaluation of the specimen diagnosed the lesion as an anaplastic astrocytoma.

On the 10th postsurgical day, the patient complained of right upper extremity weakness. A physical examination revealed right shoulder abduction power decreased to grade III. Thereafter, her neurologic status rapidly deteriorated and right shoulder flexion and abduction power was only grade I on the next day. A follow-up MRI was performed to rule out postoperative delayed hemorrhage, infarction or tumor progression. The residual mass appeared more expanded, and the longitudinal extent of abnormal high T2 signal area was greater (Fig. 1F). On the 11th

postsurgical day, she underwent a laminectomy and subtotal removal of the tumor to decompress the spinal canal. The final pathologic examination confirmed the tumor as a glioblastoma having 14 mitoses per 10 high-power-fields (Fig. 1G). Afterward, she underwent low dose concurrent chemoradiation therapy at a total dose of 3060 cGy divided into 17 fractions at the C2 to C4 level as well as maintenance-chemotherapy. However, follow-up MRIs showed a gradual increase of the extent of the abnormally high T2 signal intensity. The lesion extended from the lower medulla oblongata to the cord at the T2 level on the latest MRI taken in February, 2011.

## DISCUSSION

To be considered as a radiation-induced tumor, the lesion must meet the following criteria, the lesion must occur within or at the margin of the previously irradiated field, there must be a sufficient latency period from irradiation to tumor development, the new lesion must be different histologically and molecularly from the primary lesion, and the patient must not have pathologies favoring the

development of tumors. Our case arrived at a diagnosis as a radiation-induced tumor meeting these criteria. Following a biopsy-proven diagnosis of rhabdomyosarcoma, she received 4500 cGy of radiation to the neck. A latency period of thirteen years passed until the development of the intramedullary cervical cord lesion. The lesion was found to be high grade glioma.

Radiation-induced gliomas of the spinal cord are extremely rare; with only seven cases have been reported (1-3). The characteristics of the reported cases in addition to the present case are summarized in Table 1. It is interesting that half of radiation-induced spinal cord gliomas were followed by radiotherapy for treatment of Hodgkin's disease. The other cases developed after radiotherapy for medullomyoblastoma, thyroid cancer, rhabdomyosarcoma, and after multiple chest fluoroscopies in tuberculosis (1-3). Irradiation was delivered in young adults ranging in age from 19 to 30 years, except for two cases of medullomyoblastoma and rhabdomyosarcoma who were irradiated at three and four years old, respectively. The mean patient age at the discovery of the secondary tumor development was 30.3 years (range, 17-48 years). The mean latency period was 11.7 years (range, 3-25 years), which is comparable to the mean latency period of 9.2 to 16 years in radiation-induced gliomas in the brain (4). The mean total radiation dose was 4080 cGy (range, 3000-5500 cGy), which was measured with the mean doses of seven cases, excluding one case with unknown total radiation dose.

It is notable that a latency period is shorter in patients with Hodgkin's disease (mean 5.5 years) than those

with other solid tumors (mean 19.5 years) ( $p = 0.02$  by independent sample  $t$  test), even though the total radiation dose in Hodgkin's disease (mean 4000 cGy) was not different from that of other solid tumors (mean 4166 cGy). The effect of additional chemotherapy on a latency period is not evident because two of the four patients with Hodgkin's disease had undergone chemotherapy, whereas the others had not. To our knowledge, there is no report on the relationship between a short latency of secondary central nervous system tumors and Hodgkin's disease. Compromised immune function in Hodgkin's disease might play a role in the relatively early development of the tumor. However, a larger number of cases should be collected to see whether primary disease, chemotherapy or other parameter, such as patient age, affect a latency period of secondary spinal cord tumors.

Considering that the reported total radiation dose inducing spinal cord tumors is around 4000 cGy, the effect of additional radiation from CT scans and radiographs in our case may be minimal because the CT dose index for pediatric head and neck single-phase CT is of a few dozen mGy or much lesser. Even in that case, the effort to minimize radiation exposure from diagnostic imaging should be paid, especially in pediatric patients who have a higher sensitivity to radiation and longer survival. In addition, a much lesser dose than the therapeutic radiation dose pose a risk to induce a tumor in the spinal cord as shown in Steinbok's report (5) of low grade astrocytoma after multiple fluoroscopies for artificial pneumothorax in the treatment of pulmonary tuberculosis. The exact radiation dose was

**Table 1. Summary of Radiation-Induced Spinal Cord Tumors**

Authors	Publication (yrs)	Age at Radiation (yrs)	Primary Disease	Treatment of Primary Disease	Radiation Dose (Gy)	Latency (yrs)	Tumor Location	Tumor Type
Clifton et al.	1980	21	Hodgkin disease	RT	50	6	Cervicothoracic	Glioblastoma
Steinbok	1980	20-23	Pulmonary tuberculosis	Artificial pneumothorax	Unknown	25	Cervicothoracic	LG astrocytoma
Marus et al.	1986	19	Thyroid cancer	RT	45-55	23	Thoracic	Anaplastic astrocytoma
Bazan et al.	1990	19	Hodgkin disease	RT	40	7	Cervical	Astrocytoma Grade II-III
Grabb et al.	1996	3	Medullomyoblastoma	Surgery + RT	30	17	Cervical	Anaplastic astrocytoma
Riffaud et al.	2006	30	Hodgkin disease	RT + CTx	40	9	Cervicothoracic	Anaplastic glioma
Ng et al.	2007	23	Hodgkin disease	RT + CTx	30.6	3	Thoracic	Glioblastoma
Present case	2010	4	Rhabdomyosarcoma	RT + CTx	45	13	Cervical	Glioblastoma

**Note.**— LG = low grade, RT = radiation therapy, CTx = chemotherapy

not documented in the report. However, according to the reports on the radiation dose during artificial pneumothorax treatment, the radiation dose per one pneumothorax was estimated as 10 rads (cGy) in the back skin, 3 rads in the lung and 1 rad in the breast with an average time of one minute per one fluoroscopy (6), and most patients had received more than 100 times radiation dose from the fluoroscopies (7). In addition, in the large study about lung cancer mortality risk after multiple chest fluoroscopies including more than 25000 tuberculosis patients, a mean radiation dose was estimated to be 102 cGy in the lung (8). Based on the previous reports, we roughly estimated the total radiation dose for multiple fluoroscopies for artificial pneumothorax to be around 1000 cGy in the back skin, and much less in the spinal cord. This relatively lower radiation dose also caused secondary tumor in the spinal cord.

MRI findings of radiation-induced spinal cord gliomas were similar between the reported cases. In all cases, the lesion was shown as a diffuse enlargement of the spinal cord rather than a well-demarcated mass (1-3). T2WI showed relatively homogeneous hyperintensity, and some had internal cystic portions due to necrosis (2). After an intravenous injection of gadolinium agent, various findings of enhancement were observed; a few discrete enhancing foci within the lesion (2), diffuse homogenous enhancement (1), no enhancement (3), combined multiple stippled and discrete nodular enhancement with peripheral rim enhancement (present case). The MRI findings mentioned above may be nonspecific. Radiation myelitis overlaps with radiation-induced glioma regarding the MRI findings (9, 10), which make differentiation of the two impossible. The following reported MRI findings of radiation myelitis: diffuse cord enlargement, hyperintensity of the involved area on T2WI, one or multiple foci of discrete enhancement, or peripheral ring-like enhancement (9, 11). Therefore, when meeting an intramedullary lesion within the field prior radiotherapy, we should consider the various possibilities such as radiation myelitis, recurrent primary tumor, as well as secondary tumor. Radiation myelitis is a more common clinical condition and generally develops earlier in life (typically 6-24 months following radiotherapy) than secondary tumors (9). However, a long latency period (up to 13 years) has also been reported (10). Even [18F] 2-fluoro-2-deoxyglucose (FDG)-positron emission tomography may not be effective in differentiating these conditions because increased FDG uptake is also observed in myelitis due to the increased glucose demand of damaged

tissue (12). Therefore, pathologic confirmation is needed for such lesions.

Secondary spinal cord gliomas have a poor clinical outcome, and half of the patients have expired within a year after diagnosis. This may be partly due to their high histological grade. Most reported radiation-induced spinal cord gliomas, including our case, were high grade gliomas of WHO grade III or IV, and only one case was low grade astrocytoma. Moreover, intrinsic resistance to treatment and limited application of aggressive treatment also may play a role in poor prognosis (1, 3).

We present a case of radiation-induced spinal cord glioblastoma in status post-radiotherapy of nasopharyngeal rhabdomyosarcoma after a latency of thirteen years with a detailed description of MRI findings.

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