

## Case Report

# Radiation-Induced Glioblastoma Multiforme in a Remitted Acute Lymphocytic Leukemia Patient

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Radiation therapy has been widely applied for cancer treatment. Childhood acute lymphocytic leukemia (ALL), characterized by frequent central nervous system involvement, is a well documented disease for the effect of prophylactic cranio-spinal irradiation. Irradiation, however, acts as an oncogenic factor as a delayed effect and it is rare that glioblastoma multiforme develops during the remission period of ALL. We experienced a pediatric radiation-induced GBM patient which developed during the remission period of ALL, who were primarily treated with chemotherapeutic agents and brain radiation therapy for the prevention of central nervous system (CNS) relapse. Additionally, we reviewed the related literature regarding on the effects of brain irradiation in childhood and on the prognosis of radiation induced GBM.

**Key Words :** Radiation · Glioblastoma multiforme · Acute lymphocytic leukemia.

## INTRODUCTION

Radiation, since its first application for cancers in 1889<sup>19)</sup>, has been a relatively well tolerated and simple, yet powerful means of tumor management. Brain tumors are not exclusive ever since the development of high energy generators such as linac and cobalt-60 unit. Although the radiation is not deleterious immediately, it may induce serious side effects such as radiation-induced necrosis, radiation-related arteriopathy or tumorigenesis apart from the beneficial effects on primary target neoplasm. Post-radiation tumor, such as fibrosarcoma of the central nervous system (CNS) was first reported by Mann et al.<sup>11)</sup> and the role of radiation on tumorigenesis of the brain was documented for the first time by Modan et al.<sup>13)</sup>. From thence, there have been anecdotally reported cases of radiation-induced CNS tumors<sup>12,22,27)</sup>. However, malignant gliomas occurring in acute lymphocytic leukemia (ALL) pediatric patients on maintenance stage after complete remission have been reported very rarely worldwide. We report a pediatric CNS ALL patient, who had undergone whole brain radiation therapy (WBRT), ended up with development of glioblastoma multiforme (GBM) 6 years after the brain radiation therapy with the related literature reviews.

## CASE REPORT

A 17-year-old female patient admitted with complaints of speech disturbance and right side weakness. She had been previously diagnosed as ALL 10 years before, and was given chemotherapy according to Children's Cancer Group (CCG) 1881 trial protocol administrating prednisolone, vincristine, methotrexate, asparaginase and mercaptopurine. This brought up complete remission proven from serial bone marrow aspiration examinations. Forty-four months after the primary chemotherapy, CNS relapse was suspected from periodically planned cerebrospinal fluid cytopsin studies. Further chemotherapy following CCG 1967 trial protocol, intrathecal triple therapy administrating methotrexate, cytarabine and hydrocortisone and WBRT of 19.5 Gy was applied. Her general condition was maintained fairly well thereafter, until the development of headache, vomiting and left side weakness at one month after the beginning of chemotherapy. Brain magnetic resonance imaging (MRI) revealed intracerebral hemorrhage at right parieto-occipital lobe and thalamus (Fig. 1). The patient recovered with conservative treatment. She had only mild hemiparesis of left extremities and was maintained at remitted status of ALL thereafter.

At post-irradiation 6 years, the patient deteriorated neurologically having motor dysphasia and right hemiparesis. The brain MRI showed a large 62×55×33 mm sized irregularly enhanced cystic mass at left frontal lobe which was downward compressing lateral ventricle and had mixed signal intensities with peritumoral edema (Fig. 2). A craniotomy and near total tumor removal was performed under the guidance of functional neuro-navigation

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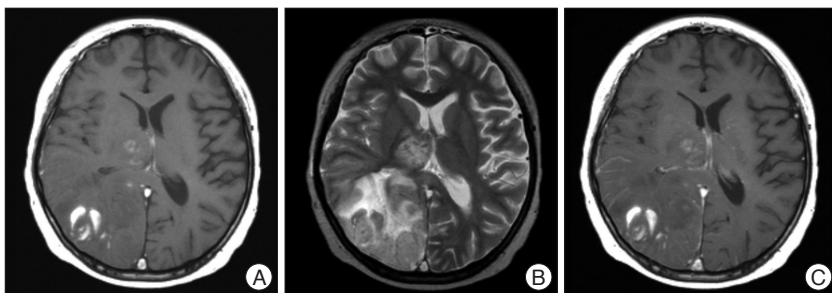
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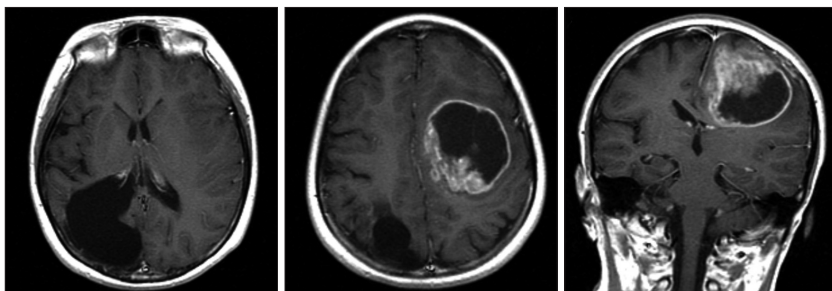
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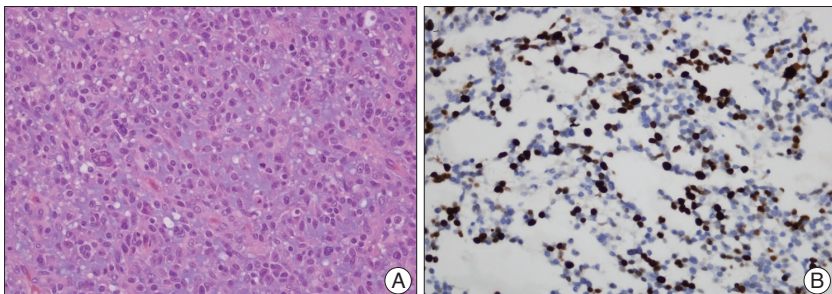
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**Fig. 1.** Brain MRI at one month after initiation of prophylactic irradiation and intrathecal methotrexate injection. Axial T1WI (A), T2WI (B) and Gd-enhanced T1WI (C) shows mixed signal intensities with slightly enhanced lesions at right parietal lobe and thalamus suggesting intracerebral hemorrhage with diffuse perilesional edema. MRI : magnetic resonance imaging.



**Fig. 2.** Brain MRI at 6 years post-irradiation. A 5.6×5.8 cm sized ring-enhanced large cystic tumor located at left frontal lobe with mass effect to adjacent ventricles and with peritumoral edema. Cerebromalatic change is visible at right parietal lobe due to previous intracranial hemorrhage. MRI : magnetic resonance imaging.



**Fig. 3.** H&E staining (×400). Cellular tumor tissue composed of pleomorphic astrocytic tumor cells with marked nuclear atypia and brisk mitotic activity are observed. Prominent microvascular proliferation is also noted. (A) Ki-67 immunohistochemical staining (×400) reveals high expression which means high proliferation (B).

system with the incorporation of fused diffusion tensor images in an attempt to minimize injuring nerve fibers of corticospinal tract during surgery.

Histopathologically, the lesion was diagnosed as a GBM which was glial fibrillary acidic protein positive and showed 40% of Ki-67 index (Fig. 3). According to the pathologic measures, there were no specific differences from that of the de novo GBM specimens. The post-operative course was uneventful with recovery from right hemiparesis. At post-operative 3 weeks, temozolomide was administered in concurrence with 40 Gy of WBRT. The radiation dose was reduced because she already has had prophylactic brain irradiation for CNS relapse of ALL. Seven months after the operation, her right hemiparesis aggravated and subsequent brain MRI revealed regional recurrence with evidences of

increased intracranial pressure. She underwent decompressive craniectomy and radical tumor removal once more with GLIADEL® Wafer placement *in situ*. However, she did not tolerate thereafter and died 4 months later.

## DISCUSSION

The treatments of ALL have been interrupted with the high rate of occurrence of CNS leukemia which heralds systemic relapse<sup>8</sup>). Radiation therapy, in concordance with chemotherapeutic agents, has been well known to be one of the prophylactic methods to ascertain long-term disease free survival for the childhood ALL patients. However, when the radiation itself acts as an oncogenic factor, especially for the occurrence of GBM, subsequent treatment of the tumor becomes even more troublesome.

Secondary brain tumor rarely occurs after brain radiation therapy although adverse effects such as radiation necrosis can result from the radiation itself<sup>22</sup>). Radiation and its oncogenic effects were reported in human for the first time by Jones<sup>9</sup>, Saenger et al.<sup>20</sup> and Mann et al.<sup>11</sup> in 1960s. Recently, sarcomas and meningiomas have been measured to be the most frequent radiation-induced brain tumors<sup>7,8</sup>). GBM, despite a most frequently occurring de novo brain tumor<sup>23</sup>), its development from radiation effect have been reported very rarely worldwide. Moreover, its occurrence in ALL patients has been reported even

scarcely. Salvati et al.<sup>22</sup>) analyzed their 16 cases and previously reported cases of radiation-induced GBM and measured the frequency among all GBM to be 1.3%.

Radiation-induced GBM in human ALL patient was reported by Chung et al.<sup>4</sup>) in 1981 for the first time. In that report, a 2-year-old boy received systemic chemotherapy for ALL and CNS irradiation along with intrathecal methotrexate for CNS prophylaxis. Five years later, GBM with a large cyst developed at left parietal area while ALL was in remission. The patient underwent cyst aspiration and subsequent brain radiation therapy (40 Gy/4 weeks to whole brain followed by 10 Gy/1 week to gross tumor with reduced fields) but died at 10 months from the diagnosis of the tumor. Since then, there have been several reports on the radiation-induced GBM in remitted ALL patients (Table 1)<sup>6,12,14,21,24,25,29</sup>).

Table 1. Reported cases and presenting case of radiation-induced GBM in ALL patients

Authors	Year	Age/Sex	Radiation dose (Gy)	Intrathecal MTX	Occurrence of GBM after RT (months)	Death from diagnosis of GBM (months)	Surgery for GBM	Adjuvant therapy for GBM	Patient status after treatment for GBM
Joh et al. (Presenting case)	2011	17/F	19.5	12 mg/m <sup>2</sup>	72	11	Near total removal and radical excision with GLIADEL® Wafer placement for recurrence	40 Gy of RT and oral TMZ	Neurological status improved after first operation and subsequent adjuvant therapy but progressively worsened after second operation
Menon et al.	2007	4/F	18	12 mg/m <sup>2</sup>	11	15	Radical excision	45 Gy of RT over 25 fractions and oral TMZ	Died 2 months after RT and TMZ
Borgmann et al.	2007	8.5/F	12	12 mg	64	14	†	RT (dose NR)	Asymptomatic
Symss et al.	2006	4/M	12	12 doses	34	†	Stereotactic biopsy	External beam radiation (astrocytoma)	Asymptomatic at 6 months after RT
Yaris et al.	2005	13/M	18	†	72	6	Partial resection	30 Gy of RT at tumor location+CCNU, vincristin and prednisolone	Neurological status progressively worsened despite surgery, RT & CTx
Shah et al.	2004	11/M	18	12 doses	59	†	CT guided stereotactic craniotomy and partial excision	45 Gy of RT	†
Muzumdar et al.	1999	12/M	20	12 mg/M2 weekly	72	*	Gross total resection	45 Gy of RT in 25 fractions over 40 days+vincristine and CCNU for 2 mo	Healthy at 2 months after RT and CTx
Salvati et al.	1991	18/M	24	†	73	5	CT guided stereotactic biopsy	Tx for edema only	†
Fontana et al.	1987	17/M	24	0.2 mg/kg monthly for 2 years	132	*	Gross total resection	†	Healthy at 6 months after surgery
					132	11	Biopsy only	30.5 Gy of RT	Radiologic improvement
Chung et al.	1981	7/M	24	0.2 mg/kg monthly for 2 years (discontinued after 15 doses d/t seizure)	120	*	Biopsy only	50 Gy of RT followed by an other 50 Gy for grown tumor	Symptomatic deterioration despite radiologic improvement
					63	10	Cystic fluid aspiration followed by mass removal	40Gy/4 weeks to whole brain followed by 10 Gy/1 week to gross tumor with reduced fields	Significant radiologic and symptomatic improvement

\*Alive when the paper was written, †Not specified within the article. RT : radiation therapy, MTX : methotrexate, TMZ : temozolomide, CT : computed tomography, CTx : chemotherapy, GBM : glioblastoma multiforme, ALL : acute lymphocytic leukemia

Reviewing these articles, males were predominant giving the male/female ration of 11 : 2. Although there have been reports postulating that de novo GBM has a slight male preponderance<sup>17,26</sup>), it is interesting that these reports on radiation-induced GBM in ALL patients are mostly male, though our patient is a female. The mean duration from the brain radiation therapy to the development of GBM was 72.3 months (range 11-132). This is a much shorter duration compared with radiation-induced tumors from other primary pathologies, previously reported to be 109-132 months<sup>16,28</sup>). The mean duration from the diagnosis of GBM to death was 10.2 months (range 5-15) after surgical and radiological treatments. This duration is also comparatively shorter than previous reports on measuring the overall survival of the radiation-associated GBM of any kind and de novo GBM, which were treated with multimodality tools, to be 20.1 months and 15.2 months respectively<sup>22</sup>). The patient presented in this paper had a period of 72 months from the brain radiation to the development of GBM and there was only 7 months from the first operation until the regional tumor recurrence. After the first operation, she was treated with concomitant chemo-radiation therapy incorporating temozolomide as the chemotherapeutic agent, but only to have no effect on prevention of the recurrence. Secondary tumor resection and GLI-ADEL<sup>®</sup> Wafer placement *in situ*, the last resort, which was not tried in previous reports, was of no effect in controlling tumor growth or prolonging survival and died only after 4 months from then, measuring the overall survival to be 11 months.

The causative factors for development of radiation induced GBM is still not clearly verified. Irradiation dose, underlying disease, patient's general condition, age at irradiation, primary tissue pathology and combined chemotherapy may all contribute to the occurrence to certain extents. Concerning the radiation dose itself, there have been reports postulating that prophylactic irradiation of higher dose (usually more than 30 Gy) gives rise to higher risk of malignant brain tumor occurrence compared to that of lower doses (less than 18 Gy). On the other way, there have been counterproposals suggesting that radiation dose not always give rise to higher rate of secondary tumor development because when the radiation dosage is too high, oncogenic cells may also be eliminated<sup>22</sup>). Interestingly, in this presenting case and in all of the cases listed in Table 1, irradiation doses were in between 12 to 24 Gy. Therefore, as mentioned above, radiation itself might not be the sole contributing factor in the development of radiation-induced GBM. Given that 13% of all secondary neoplasms in ALL patients are brain tumors of any kind<sup>10</sup>), in which the brain being the most common location to develop secondary tumors in ALL patients, those with ALL might be genetically susceptible to the development of gliomas<sup>1,15,18</sup>).

Histopathologically, GBM as a primary tumor and radiation-induced GBM are not different. Donson et al.<sup>5</sup>), from their molecular analysis of 5 radiation-induced GBMs, demonstrated greater homogeneity of gene expression than de novo GBM in

pediatric patients. On the other hand, Brat et al.<sup>1)</sup> could not conclude the definitive molecular difference between the two groups. From our case of a radiation-induced GBM, we also could not find histopathologic differences, in which the diagnosis of radiation-induced GBM had to be dependent solely on clinical evidences. Cahan et al. defined the radiation-induced GBM should satisfy the following criteria; 1) the tumor must arise within the area of previous irradiation; 2) a sufficient latency period (measured in years) should be present between radiation and onset of tumor growth; 3) there must be histopathologic difference between the primary tumor and newly developed tumor; and 4) the patient must be free from diseases prone to carcinogenesis, such as Recklinghausen's disease, Li-Fraumeni's disease, tuberous sclerosis, xeroderma pigmentosum or retinoblastoma. In our case also, the pathologic finding is not different from primary GBM, and clinically, the patient matches the above 4 criteria.

GBM developed after irradiation have been known to have less tumor control rate and more aggressive behavior compared to that of the de novo GBM, even after the tumor is being treated with active medical and surgical means. Moreover, severity of the progress of gliomas, when developed after irradiation, is not related to radiation dose received. Up to date, there are no much clinically efficient management protocols extending survival rate for radiation-induced GBM and when it is related to ALL, prognosis is even worse. More trials with active surgical manipulations, in combination with medically possible strategies and also with other advanced therapeutic means should be carried out to gain improved clinical outcomes.

## CONCLUSION

We experienced a highly malignant radiation-induced GBM, unresponsive to active surgical and medical treatment. Although radiation at present is one of the best applicable tools to prevent progression of various disease entities in childhood, personnel involved should always be aware that it can also be harmful. When radiation-induced GBM is associated with ALL, the prognosis might be even worse with less responsiveness to multimodality treatments. Therefore, radiation therapy, when it has to be incorporated in the treatment of ALL patient, careful planning of the treatment protocol and judicious follow-up is needed.

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