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 cytospin 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.
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. 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. Radiation and its oncogenic effects were reported in human for the first time by Jones, Saenger et al. and Mann et al. in 1960s. Recently, sarcomas and meningiomas have been measured to be the most frequent radiation-induced brain tumors. GBM, despite a most frequently occurring de novo brain tumor, 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. 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. 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).

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 system with the incorporation of fused diffusion tensor images in an attempt to minimize injuring nerve fibers of corticospinal tract during surgery.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Age/Sex</th>
<th>Radiation dose (Gy)</th>
<th>Intrathecal MTX</th>
<th>Occurrence of GBM after RT (months)</th>
<th>Death from diagnosis of GBM (months)</th>
<th>Surgery for GBM</th>
<th>Adjuvant therapy for GBM</th>
<th>Patient status after treatment for GBM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joh et al.</td>
<td>2011</td>
<td>17/F</td>
<td>19.5</td>
<td>12 mg/m²</td>
<td>72</td>
<td>11</td>
<td>Near total removal and radical excision with GLIADEL Wafel placement for recurrence</td>
<td>40 Gy of RT and oral TMZ</td>
<td>Neurological status improved after first operation and subsequent adjuvant therapy but progressively worsened after second operation</td>
</tr>
<tr>
<td>Menon et al.</td>
<td>2007</td>
<td>4/F</td>
<td>18</td>
<td>12 mg/m²</td>
<td>11</td>
<td>15</td>
<td>Radical excision</td>
<td>45 Gy of RT over 25 fractions and oral TMZ</td>
<td>Died 2 months after RT and TMZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6/M</td>
<td></td>
<td></td>
<td>36</td>
<td>*</td>
<td>Radical excision</td>
<td>RT (dose NR)</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10/M</td>
<td></td>
<td></td>
<td>72</td>
<td>*</td>
<td>Radical excision (Astrocytoma) Radar excision (transformed GBM)</td>
<td>External beam radiation (astrocytoma) TMZ (transformed GBM)</td>
<td>Asymptomatic at 6 months after RT</td>
</tr>
<tr>
<td>Borgmann et al.</td>
<td>2007</td>
<td>8.5/F</td>
<td>12</td>
<td>12 mg</td>
<td>64</td>
<td>14</td>
<td>† Stereotactic biopsy</td>
<td>† Stereotactic biopsy</td>
<td>† Stereotactic biopsy</td>
</tr>
<tr>
<td>Symss et al.</td>
<td>2006</td>
<td>4/M</td>
<td>12</td>
<td>12 doses</td>
<td>34</td>
<td>†</td>
<td>Partial resection</td>
<td>† Partial resection</td>
<td>† Partial resection</td>
</tr>
<tr>
<td>Yarls et al.</td>
<td>2005</td>
<td>13/M</td>
<td></td>
<td></td>
<td>72</td>
<td>6</td>
<td>† CT guided stereotactic craniotomy and partial excision</td>
<td>45 Gy of RT</td>
<td>Neurological status progressively worsened despite surgery, RT &amp; CTx</td>
</tr>
<tr>
<td>Shah et al.</td>
<td>2004</td>
<td>11/M</td>
<td>18</td>
<td>12 doses</td>
<td>59</td>
<td>†</td>
<td>† CT guided stereotactic craniotomy and partial excision</td>
<td>† CT guided stereotactic craniotomy and partial excision</td>
<td>† CT guided stereotactic craniotomy and partial excision</td>
</tr>
<tr>
<td>Muzumdar et al.</td>
<td>1999</td>
<td>12/M</td>
<td>20</td>
<td>12 mg/M2 weekly</td>
<td>72</td>
<td>*</td>
<td>Gross total resection</td>
<td>45 Gy of RT in 25 fractions over 40 days+ vincristine and CCNU for 2 mo</td>
<td>Healthy at 2 months after RT and CTx</td>
</tr>
<tr>
<td>Salvati et al.</td>
<td>1991</td>
<td>18/M</td>
<td></td>
<td></td>
<td>73</td>
<td>5</td>
<td>CT guided stereotactic biopsy</td>
<td>Tx for edema only</td>
<td>† CT guided stereotactic biopsy</td>
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<tr>
<td>Fontana et al.</td>
<td>1987</td>
<td>17/M</td>
<td>0.2 mg/kg monthly</td>
<td></td>
<td>132</td>
<td>*</td>
<td>Gross total resection</td>
<td>30 Gy of RT</td>
<td>Healthy at 6 months after surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13/M</td>
<td>0.2 mg/kg monthly</td>
<td></td>
<td>120</td>
<td>*</td>
<td>Biopsy only</td>
<td>50 Gy of RT followed by an other 50 Gy for grown tumor</td>
<td>Symptomatic deterioration despite radiologic improvement</td>
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<td></td>
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<td>for 2 years</td>
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<td>(discontinued after</td>
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<td>15 does due to seizure)</td>
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<tr>
<td>Chung et al.</td>
<td>1981</td>
<td>7/M</td>
<td>24</td>
<td>12 mg/M2 (7.8 mg) twice weekly for 6 doses</td>
<td>63</td>
<td>10</td>
<td>Cystic fluid aspiration followed by mass removal</td>
<td>40 Gy/4 weeks to whole brain followed by 10 Gy/1 week to gross tumor with reduced fields</td>
<td>Significant radiologic and symptomatic improvement</td>
</tr>
</tbody>
</table>

*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, 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. 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. 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 GLIADEL 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. 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, 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.

Histopathologically, GBM as a primary tumor and radiation-induced GBM are not different. Donson et al. 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. 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 Rechlinghausen’s disease, Li-Fraumani’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.

**References**