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CASE REPORT

Three case reports of radiation-induced glioblastoma after complete remission of acute lymphoblastic leukemia

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Abstract
Radiation therapy is sometimes performed to control intracranial acute lymphoblastic leukemia (ALL), but may lead to radiation-induced malignant glioma. The clinical, radiological, histological, and molecular findings are described of three cases of radiation-induced glioblastoma after the treatment for ALL. They received radiation therapy at age 6–8 years. The latency from radiation therapy to the onset of radiation-induced glioblastoma was 5–10 years. Magnetic resonance imaging demonstrated diffuse lesions with multiple small enhanced lesions in all cases. Histological examination showed that the tumors consisted of mainly small round astrocytic atypical cells in one case, and astrocytic atypical cells with elongated cytoplasm and nuclear pleomorphism with small cell component in two cases. Microvascular proliferation was present in all cases. Immunohistochemical analysis for B-Raf V600E, and mutational analysis for the isocitrate dehydrogenase (IDH) 1, IDH2, and H3F3A gene revealed the wild-type alleles in all three cases. The integrated diagnoses were IDH wild-type glioblastoma, and local irradiation and concomitant temozolomide were performed. After the initial treatment, significant shrinkage of the diffuse lesion and enhanced lesion was found in all cases. Radiation-induced glioblastoma occurring after the treatment for ALL had unique clinical, radiological, histological, and molecular characteristics in our three cases.

Keywords Acute lymphoblastic leukemia · Radiation-induced glioblastoma · Clinicopathological findings

Introduction

Acute lymphoblastic leukemia (ALL) is the most common neoplasm in childhood, but more than half of patients who achieved complete remission with chemotherapy suffered recurrence in the central nervous system (CNS) [1]. Prophylactic therapy with craniospinal irradiation and CNS-directed chemotherapy was introduced in the early 1970s, which significantly improved the prognosis for pediatric ALL [2]. However, cranial irradiation in childhood is associated with severe side effects including developmental and endocrinal disorders, radiation-induced necrosis, vascular complications, and secondary neoplasm [3–33]. Risk-stratified effective and intensive chemotherapy, and both intrathecal and systemic CNS-directed treatment have improved 5-year event-free survival rates for childhood ALL to > 85% [34–36]. Craniospinal irradiation is now limited to patients with CNS involvement at initial onset (8.7%) or relapse (2.5%) [35]. Consequently, improvements in intensive chemotherapy have eliminated the necessity for craniospinal irradiation therapy in most cases, but radiation therapy remains indispensable in the treatment of ALL.

Radiation-induced neoplasm is a relatively rare complication of radiation therapy. The cumulative incidence of intracranial tumor is 3.0% at 30 years, and cranial irradiation carries the risk for the formation of radiation-induced intracranial tumor [15]. Furthermore, radiation-induced malignant glioma may occur after the treatment for ALL [4, 5, 9–18, 20, 22–33]. Some clinical aspects including the frequency, primary neoplasms, and latency of ALL-related

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glioblastoma and other central nervous system (CNS) tumors have been reported [5, 6, 31]. The cumulative incidence of all intra-cranial tumors at 20 years is 1.39%, and histology of secondary tumors was high grade glioma in 10, low grade glioma in 1, and meningioma in 11 [5]. Risk factors for developing secondary CNS tumors was the presence of CNS leukemia, cranial irradiation in dose dependent manner, and less than 6 years [5]. Four of 1612 cases (0.25%) with acute lymphoblastic leukemia developed radiation-induced glioblastoma with median follow-up period of 15.9 years [5]. The five most frequent primary lesions of radiation-induced malignant glioma were ALL (31.8%), medulloblastoma (13%), pituitary adenoma (10.8%), craniopharyngioma (8%), and tinea capitis (4%) [4]. However, the radiological, histological, molecular characteristics, and treatment outcomes after radiation therapy and temozolomide (TMZ) remain unclear due to the rarity of ALL-related glioblastoma.

We present the clinical, radiological, histological, and molecular findings of three cases of radiation-induced glioblastoma after radiation therapy for ALL.

Materials and methods

All histological materials were immediately fixed in 10% buffered formalin (Wako, Osaka, Japan) at room temperature for several days, and cut into 2-μm thick paraffin sections. Immunohistochemical examination was performed using automated immunostaining systems with Ventana Benchmark ULTRA (Roche, Basel, Switzerland) for glial fibrillary acidic protein (GFAP), vimentin, TP53, p16, alpha thalassemia/mental retardation syndrome X-linked (ATRX), and B-Raf (BRAF) V600E, and Autostainer Link 48 for Ki-67. The primary antibodies were rabbit monoclonal antibody for GFAP (EP672Y, Roche), vimentin (V9, Roche), and mouse monoclonal antibody for TP53 (DO-7, Roche), p16 (E6H4, Roche), ATRX (CL0537, Abcam, Cambridge, UK), BRAF (VE1, Roche), and Ki-67 (MIB-1, Aligent, Santa Clara, USA). Immunoreactivity of TP53 and Ki-67 was semi-quantified as labeling indexes by counting stained tumor cells among 1000 cells in the regions with the most immunoreactivity. The cut-off value of the labeling index was 10% for TP53 staining [37]. Immunostaining for O^6-methylguanine methyltransferase (MGMT) was performed with anti-MGMT antibody (MT3.1, Merck, Darmstadt, Germany). Antigen retrieval was accomplished for MGMT by heating in an autoclave for 5 min at 121 °C in citric acid buffer (2 mmol/L citric acid and 9 mmol/L trisodium citrate dehydrate, pH 6.0) [37].

The detection of mutation on IDH1 and IDH2 gene were performed with high resolution melting analysis with cobas z 480 system (Riche Molecular Diagnostics, Pleasanton, USA). The forward and reverse primer sequences for the IDH1 gene were 5′-CGGTCTTCAGAGAAGCCATT-3′ and 5′-CACATTATTGCCAACATGAC-3′. The forward and reverse primer sequences for the IDH2 gene were 5′-GGG GTTCAAATTCTGGTTGA-3′ and 5′-CTAGGCGAGGAG CTCCAGT-3′. The PCR conditions for amplification of IDH1 and IDH2 were as follows. 95 °C for 10 min, 50 cycles of PCR consisting of denaturation at 95 °C for 10 s, annealing at 65 − 53 °C for 10 s with touchdown method and extension at 72 °C 10 s. The detections of mutation on IDH1 and IDH2 gene were performed by 95 °C for 1 min, 40 °C for 1 min, and gradual heating from 65 to 95 °C. Genetic analysis of the H3F3 gene used DNA purified from tissue sections using a nucleic acid extraction kit (RecoverAll Total Nucleic Acid Isolation, Ambion K.K., Tokyo, Japan) following the manufacturer's instructions. Mutations of H3F3A gene was investigated using an automated gene analyzer based on the probe quench method, i-densy (Arkray, Kyoto, Japan), following the manufacturer's instructions.

Case reports

Case 1

A 2-year-old boy without familial history of neoplasm was diagnosed with ALL. He was treated with chemotherapy and achieved complete remission. He suffered recurrence of ALL in the meninges of the left cerebral hemisphere at age 8 years [18]. He received intrathecal administration of methotrexate and cytarabine, and craniospinal irradiation 18 Gy, and achieved complete remission. He presented with progressive right upper limb ataxia and severe headache at age 13 years. Magnetic resonance (MR) imaging showed diffuse lesion in the right cerebellar hemisphere and the right side of the pons, and multiple enhanced lesions in the cerebellar hemisphere and vermis (Fig. 1a). He underwent resection of the cerebellar lesion (Fig. 1b). Histologically, tumor consisted of atypical cells with elongated cytoplasm and nuclear pleomorphism in the fibrillary background (Fig. 1d). Monomorphic small cell component was also found in addition to the pleomorphic tumor cells (Fig. 1e). There was microvascular proliferation, but not necrosis (Fig. 1e). Immunohistochemical examination detected weak and focal staining for GFAP and vimentin, positive staining for ATRX and TP53, and negative staining for p16 and BRAF V600E (Table 1). MGMT was diffusely expressed (Fig. 1f). The Ki-67 labeling index was 56.7% (Fig. 1g). The tumor did not have any mutation on the IDH1/2 gene or mutation of K27M, G34R, and G34V on the H3F3A genes (Table 1). The integrated diagnosis was IDH wild-type glioblastoma.

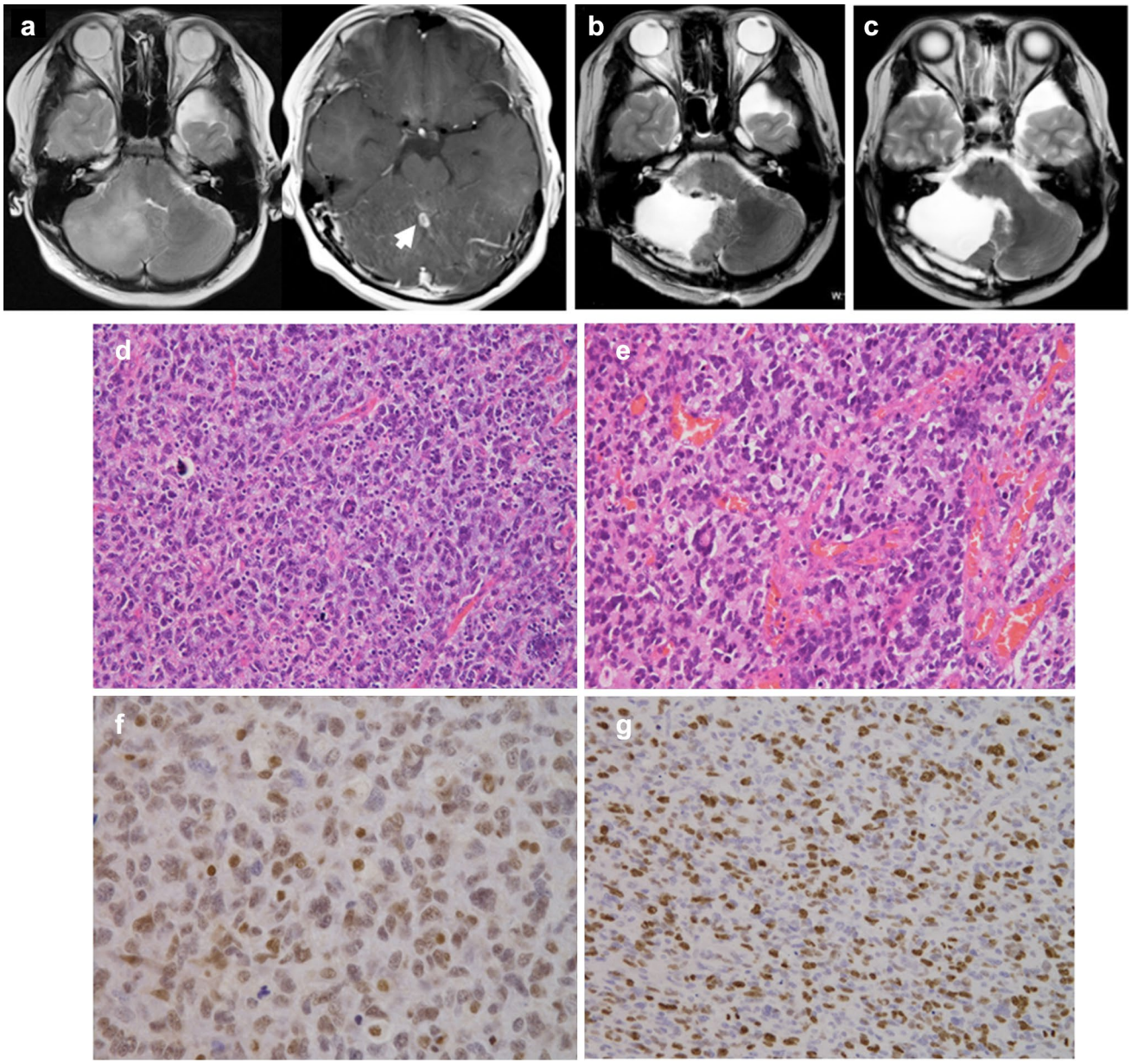

Fig. 1 Magnetic resonance (MR) images and histological findings of Case 1. **a** T2-weighted (left) and gadolinium-enhanced T1-weighted MR images (right) at the age of 13 years, demonstrating newly developed diffuse lesion in the right cerebellar hemisphere and pons, and enhanced lesion in the cerebellar vermis (arrow). T2-weighted MR images after resection of cerebellar tumor (**b**) and after initial combined radiation therapy and temozolomide (**c**), demonstrating disappearance of the postoperative residual lesion in the pons. Hematoxylin–eosin staining demonstrating that the tumor consisted of atypical cells with eosinophilic cytoplasm and nuclear polymorphism in the fibrous background (**d**), and monomorphic small round cells (**e**). Microvascular proliferations were present (**e**). Immunohistochemical examination for O^6-methylguanine methyltransferase (MGMT) (**f**) and Ki-67 (**g**), demonstrating diffuse expression of MGMT and Ki-67 labelling index of 56.7%. Origical magnification ×100 (**d**), × 200 (**e, g**), and ×400 (**f**)

He received craniospinal irradiation 30 Gy with concomitant TMZ, after which the diffuse lesion on the right side of the pons disappeared (Fig. 1c). However, he had recurrent enhanced lesion on the pons 7 months after the initial treatment [18], and he died of progressive disease 14 months after initial treatment.

Case 2

A 6-year-old girl without familial history of neoplasm was diagnosed with ALL based on positive cytology in the cerebrospinal fluid. She achieved complete remission after chemotherapy and craniospinal irradiation 12 Gy according to the Japan Association Childhood Leukemia Study Group

Table 1 Summary of immunohistochemical and molecular analysis findings of three cases of radiation-induced glioblastoma after the treatment for acute lymphoblastic leukemia

Case No.	GFAP	Vimentin	TP53	p16	ATRX	BRAF V600E	IDH1/2 gene	H3F3A[a]
1	+/−	+/−	+	−	+	−	wt	wt
2	++	++	−	+	+	−	wt	wt
3	++	++	+	+	+	−	wt	wt

+/−, weak and focal staining; +, positive staining; ++, strong staining; −, negative staining; *wt* wild-type

[a]Analyzed for K27M, G34R, and G34V mutations on the H3F3A genes

ALL-02 Protocol [38]. She presented with generalized convulsions at age 16 years. MR imaging showed diffuse lesion in the right insula, temporal, and frontal lobe (Fig. 2a), and multiple small enhanced lesions in the right temporal and parietal lobes (Fig. 2a). She underwent resection of the enhanced lesion (Fig. 2b). Histologically, the lesion consisted of mainly small neoplastic cells of high nuclear/cytoplasmic ratio with high cellularity, showing as small

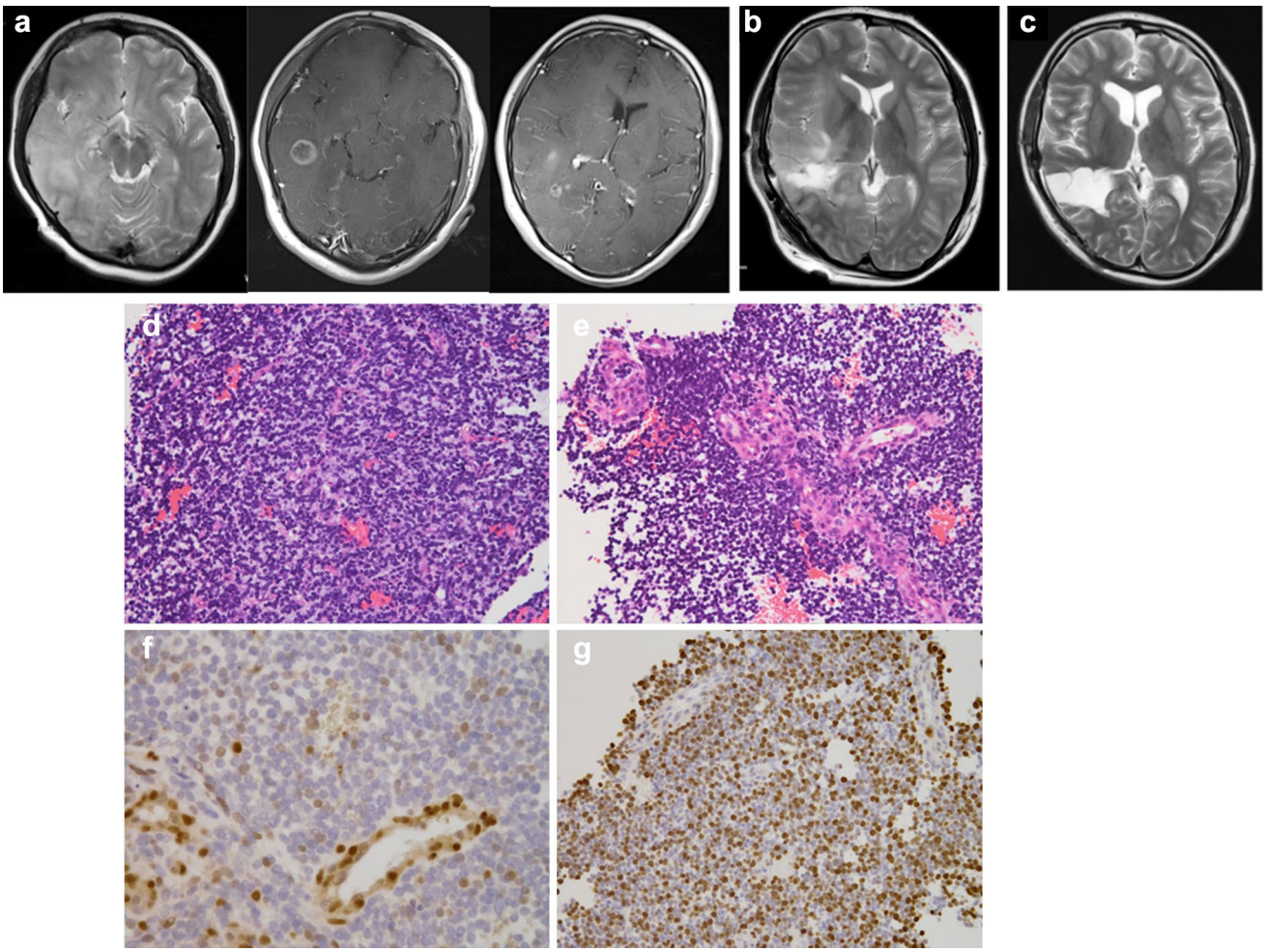

Fig. 2 MR images and histological findings of Case 2. **a** T2-weighted (left) and gadolinium-enhanced T1-weighted MR images (middle and right) at the age of 16 years, demonstrating diffuse lesion in the right insula, and frontal, temporal lobes, and enhanced lesion in the temporal and parietal lobes. T2-weighted MR images after resection of the enhanced lesion (**b**) and after initial combined radiation therapy and temozolomide (**c**), demonstrating disappearance of the postoperative residual lesion in the right cerebrum. Hematoxylin–eosin staining demonstrating that the tumor consisted of mainly small neoplastic cells of high nuclear/cytoplasmic ratio with high cellularity, showing as small cell glioblastoma-like feature (**d**), and that microvascular prolifereations were present (**e**). Immunohistochemical examination for MGMT (**f**) and Ki-67 (**g**), demonstrating weak expression of MGMT and Ki-67 labelling index of 60.0%. Original magnification ×50 (**e, g**), ×100 (**d**), ×400 (**f**)

cell glioblastoma-like feature (Fig. 2d). There was microvascular proliferation, but not necrosis (Fig. 2e). Immunohistochemical examination demonstrated strong staining for GFAP and vimentin, positive staining for p16 and ATRX, and negative staining for TP53, or BRAF V600E (Table 1). MGMT was focally and weakly expressed (Fig. 2f). The Ki-67 labeling index was 60.0% (Fig. 2g). Genetic analysis did not detect any mutation on the IDH1/2 gene or mutation of K27M, G34R, and G34V on the H3F3A genes (Table 1). The integrated diagnosis was IDH wild-type glioblastoma. She received irradiation 50 Gy to the local site with concomitant TMZ, and the diffuse lesion on the right cerebrum disappeared after 1 cycle of TMZ. She received 24 cycles of TMZ, and has remained well without recurrence for 28 months after initial treatment (Fig. 2c).

Case 3

A 7-year-old girl without familial history of neoplasm was diagnosed with ALL associated with Philadelphia chromosome. She achieved complete remission after chemotherapy, followed by bone marrow transplantation. Whole body irradiation 12 Gy, including craniospinal irradiation 12 Gy, was performed as part of the bone marrow transplantation. She presented with simple partial seizure and paresis of the face at age 16 years. MR imaging showed diffuse lesion in the right frontal and parietal lobes, and multiple enhanced lesions in the right precentral and middle frontal gyri (Fig. 3a). She underwent stereotactic biopsy of the enhanced lesion. Histologically, atypical glial cells with eosinophilic cytoplasm proliferated with high cellularity. Moderate nuclear pleomorphism and small cell component were also noted. There was microvascular proliferation, but not necrosis (Fig. 3c). Immunohistochemical examination demonstrated strong staining for GFAP and vimentin, positive staining for p16, TP53, and ATRX, and negative staining for and BRAF V600E (Table 1). MGMT was focally and weakly expressed (Fig. 3d). The Ki-67 labeling index was 45.8% (Fig. 3e). Genetic analysis did not detect any mutation on the IDH1/2 gene or mutation of K27M, G34R, and G34V on the H3F3A genes (Table 1). The integrated diagnosis was IDH wild-type glioblastoma. She received irradiation 50 Gy to the local site with concomitant TMZ. The diffuse lesion and gadolinium-enhanced lesion were significantly decreased at 1 month after the completion of initial treatment (Fig. 3b).

Discussion

This study describes the clinical course, radiological and histological findings, and molecular analysis of three cases of radiation-induced glioblastoma occurring after complete remission of ALL. In our series, the age at radiation was 8, 6, and 7-years-old. The radiation dosage was 18, 12, and 12 Gy. The latency for developing glioblastoma was 5, 9, and 10 years after irradiation. In the previous report, 34 cases with radiation-induced glioblastoma after remission of ALL have reported [4, 9–11, 13, 14, 17, 20, 22–31]. The clinical, histological, and radiological characteristics of the cases in previously report and present study were shown in Table 2. The age at radiation was 2–26 years-old (median age 5 years-old). The radiation dosage was 12–48 Gy (median dosage 19.5 Gy), and 5 (13.5%) and 11 (29.7%) of them received low dosage irradiation 12 and 18 Gy, respectively (Table 2). In this way, the clinical features of this entity were young age at radiation and low dosage radiation therapy. There are some explanations for these characteristics as follows. The low dosage irradiation 12–24 Gy were performed for the purpose of prophylaxis and treatment for CNS lesion [36], and the risk for developing radiation induced glioma were highest in younger than 5-years-old. Because the risk for radiation induced glioblastoma have linear relationship to radiation dosage over a wide range of 0–50 Gy [33], even craniospinal irradiation12 Gy could induce radiation-induced glioblastoma. Furthermore, the latency for developing glioblastoma were 3–17 years (median 9 years) (Table 2), and was shorter than radiation-induced meningioma after the treatment for ALL [31]. Radiation-induced malignant glioma after the treatment for ALL was reported to develop with significantly shorter latency than medulloblastoma and pituitary adenoma [4]. Chemotherapy, including etoposide and cyclophosphamide, may influence the development of secondary neoplasm after intensive treatment for relapsed acute lymphoblastic leukemia in childhood [19]. Such chemotherapy combined with radiation therapy may promote earlier development of glioblastoma in patients with ALL.

MR imaging demonstrated diffuse lesions on T2-weighted images with small gadolinium-enhanced lesions in all of our patients. The radiological findings have been variously described [9, 11, 14, 17, 20, 23, 25, 30] (Table 2). The report of the MR imaging findings is limited to six case report [9, 17, 20, 23, 25], and it was similar to our cases in two of six previous cases [9, 17]. Otherwise, the radiological characteristics were cyst formation in 3 of 13 cases [9, 14, 23] and multiple enhanced lesions in 7 of 13 cases [9, 14, 17] (Table 2). These changes may indicate that small multiple enhanced lesions, as observed in this series, show further progression.

Although undifferentiated histological features may be non-specific features of glioblastoma, 10 of 12 cases with radiation induced glioblastoma after the treatment of ALL had of small cell components [9, 20] (Table 2) Microvascular proliferation were found in all of our three cases and another 13 cases (Table 2). In contrast, necrosis was present only in 5 of 11

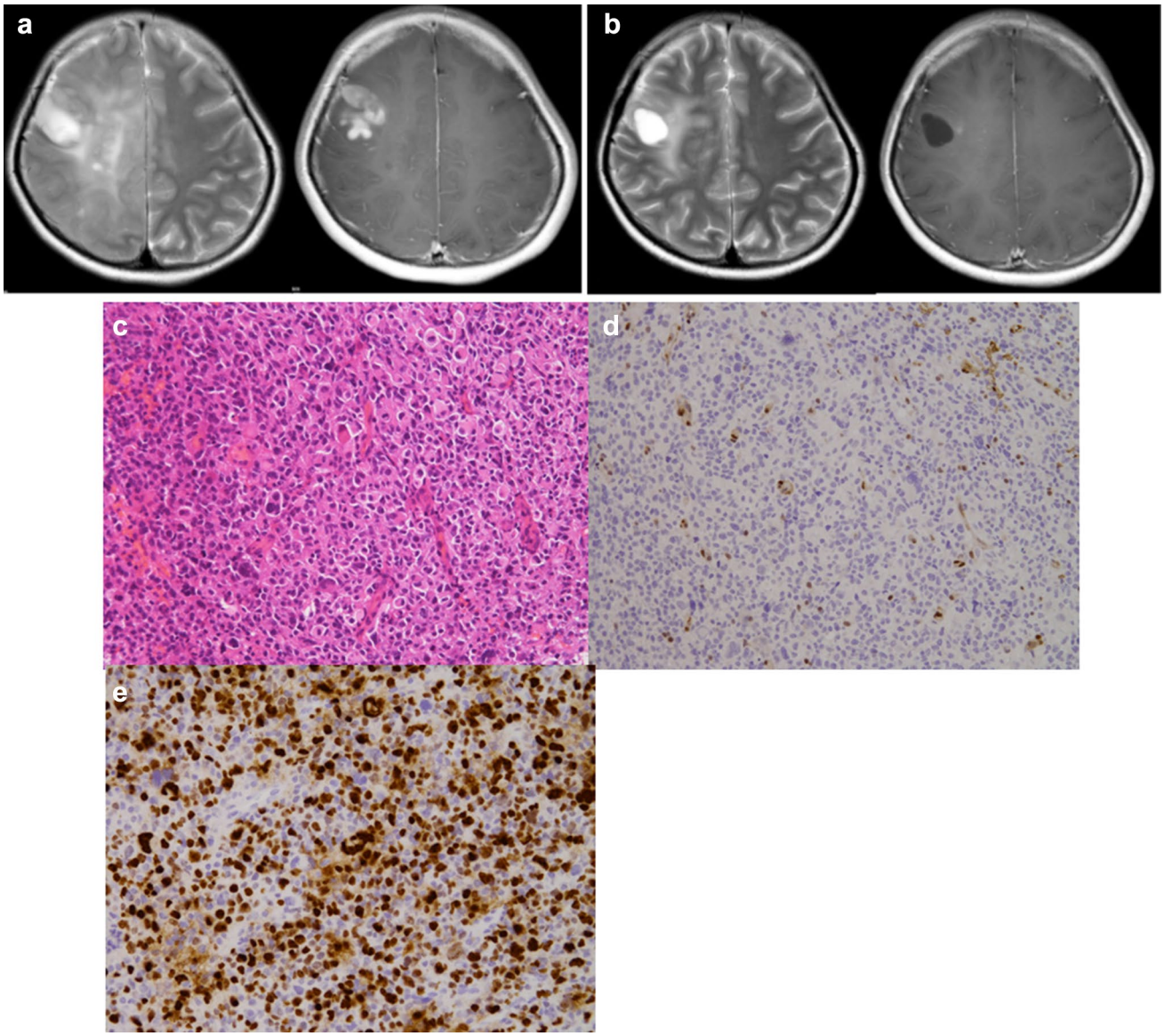

Fig. 3 MR images and histological findings of Case 3. **a** T2-weighted (left) and gadolinium-enhanced T1-weighted MR images (right) at admission, demonstrating diffuse lesion in the right frontal and parietal lobes and enhanced lesion in the precentral and middle frontal gyri. **b** T2-weighted (left) and gadolinium-enhanced T1-weighted MR images (right) 1 month after concomitant radiation therapy and chemotherapy with temozolomide, demonstrating significant shrinkage of the diffuse and enhanced lesions. **c** Hematoxylin–eosin staining demonstrating that the tumor consisted of atypical glial cells with eosinophilic cytoplasm proliferated with high cellularity. Microvascular proliferations were present. Immunohistochemical examination for MGMT (**d**) and Ki-67 (**e**), demonstrating weak expression of MGMT and Ki-67 labelling index of 45.8%. Original magnification ×100 (**c, d**), ×200 (**e**)

cases (Table 2). Other histological features were gliosarcoma [12] and giant cell glioblastoma [13]. Immunohistochemical analysis found no specific pattern of expression of various proteins in our cases, and there were few reports of immunohistochemical finding. In previous report and present cases, radiation-induced glioblastoma after ALL treatment had positive expression of TP53 in five of nine cases [20]. Recently, Germline mutations in cancer-predisposing genes were identified in 8.5% of the children and adolescents with cancer, and mutation on the p53 gene were frequently found in CNS tumor and leukemia [39]. Considering that there were five cases (13%) with short latency less than 5 years (Table 2), some cases with glioblastoma after the treatment of ALL might have cancer-predisposing germline mutation on p53. In this study, the tumors had high Ki67 labeling index. In previous reports, it ranged from 10 to 43% [20, 23]. No correlations were reported between tumor control and Ki-67 labeling index [20]. Further

Table 2 Summary of the cases with radiation induced glioblastoma after the treatment of acute lymphoblastic leukemia

References	Age at radiation/gender	Radiation dosage (Gy)	Latency (years)	Histological findings				Radiological findings
				Morphology	Necrosis	MVD	Ki67 LI (%)	
Donson et al. [22]	4/F	ND	10	ND	ND	ND	ND	ND
Fontana et al. [14]	6/M	24	11	ND	Present	Present	ND	CT: multiple solid enhanced lesion
Fontana et al. [14]	3/M	24	10	ND	ND	Present	ND	CT: multiple solid and cystic enhanced lesion
Joh et al. [23]	10/F	19.5	6	Nuclear pleomorphism	ND	Present	40	MRI: single cystic lesion
Menon et al. [11]	6/M	18	3	N.D	N.D	ND	N.D	CT: single solid enhanced lesion
Muzumdar et al. [24]	12/M	20	6	ND	ND	ND	ND	ND
Prasad et al. [25]	4/M	18	10	ND	ND	ND	ND	MRI: single solid enhanced lesion
Rimm et al. [32]	6/M	24	11	ND	ND	ND	ND	ND
Romeike et al. [20]	2/F	18	8	Small cell nuclear pleomorphism	Absent	Present	10	ND
Romeike et al. [20]	2/M	24	9	Small cell	Present	Present	10	ND
Romeike et al. [20]	2/F	18	13	Small cell nuclear pleomorphism	Present	Present	22	MRI: single solid enhanced lesion
Romeike et al. [20]	3/F	24	10	ND	ND	ND	ND	ND
Romeike et al. [20]	4/M	12	8	Small cell	Absent	Present	41	ND
Romeike et al. [20]	5/M	18	14	Small cell nuclear pleomorphism	Absent	Present	ND	ND
Romeike et al. [20]	5/M	12	10	Nuclear pleomorphism	Present	Present	43	ND
Salvati et al. [26]	10/F	24	12	ND	ND	ND	ND	ND
Salvati et al. [26]	12/M	24	6	ND	ND	ND	ND	ND
Salvati et al. [26]	10/F	24	11	ND	ND	ND	ND	ND
Salvati et al. [27]	26/M	24	11	ND	NXD	ND	ND	ND
Sanders et al. [28]	4/F	24	5	ND	ND	ND	ND	ND
Shah et al. [17]	11/M	18	5	ND	Present	Present	ND	MRI: diffuse lesion with multiple enhanced lesion
Shapiro et al. [10]	6/F	24	4	ND	ND	ND	ND	ND
Stragliotto et al. [29]	5[a]	18	3	ND	ND	ND	ND	ND
Stragliotto et al. [29]	5[a]	24	3	ND	ND	ND	ND	ND
Stragliotto et al. [29]	9.5[a]	24	2.5	ND	ND	ND	ND	ND
Stragliotto et al. [29]	5[a]	24	13	ND	ND	ND	ND	ND
Stragliotto et al. [29]	6[a]	18	7	ND	ND	ND	ND	ND
Symss et al. [30]	4/M	12	3	N.D	ND	Present	ND	CT: single solid enhanced lesion
Walter et al. [31]	15/M	24	9	ND	ND	ND	ND	ND
Walter et al. [31]	2/M	24	7.6	ND	ND	ND	ND	ND
Walter et al. [31]	2/M	18	11	N.D	ND	ND	ND	ND
Walter et al. [31]	5/M	48	5.9	ND	ND	ND	ND	ND
Wang et al. [9]	5/M	15	13	Small cell	ND	Present	ND	MRI: single cystic enhanced lesion
Wang et al. [9]	3/M	18	17	Small cell	ND	Present	ND	MRI: diffuse lesion with small enhanced lesion
Present case 1	8/M	18	5	Small cell nuclear pleomorphism	Absent	Present	56.7	MRI: diffuse lesion with small enhanced lesion
Present case 2	6/F	12	10	Small cell	Absent	Present	60.0	MRI: diffuse lesion with small enhanced lesion
Present case 3	7/F	12	9	Small cell nuclear pleomorphism	Absent	Present	45.8	MRI: diffuse lesion with small enhanced lesion

M male, *F* female, *ND* not described, *MVD* microvascular proliferation, *LI* labeling index

[a]Gender was not described

analysis may identify useful prognostic or predictive markers for this entity.

The molecular findings of radiation-induced glioblastoma after ALL treatment are unclear. This is the first report to describe the molecular findings of glioblastoma after the treatment of ALL. Somatic mutations in BRAF, IDH, and H3F3A gene are important in the gliomatogenesis of pediatric and adolescent glioblastoma [40]. None of our three cases had the mutation observed in sporadic cases. Similarly, no aberrations in IDH1 and IDH2, human telomerase reverse transcriptase promotor, H3F3A or BRAF gene were found in four cases of radiation-induced glioma which developed after radiation therapy for medulloblastoma, craniopharyngioma, primitive neuroectodermal tumor, and pituitary adenoma [21]. These findings indicate that radiation-induced glioblastoma after the treatment for ALL or other primary lesions includes aberrant pathways different to those in sporadic cases. Recently, homozygous germline mutations in the MSH6 gene were reported to lead to gliomatosis cerebri and T-cell acute lymphoblastic lymphoma in an 11-year-old female and glioblastoma in her 10-year brother [41]. Therefore, clinicians should consider the possibilities of cancer predisposing syndrome to treat malignant brain tumor after the treatment for ALL.

Our three cases were treated with irradiation to the local brain and concomitant monotherapy with TMZ. The effect of combination therapy of radiation and TMZ on radiation-induced glioblastoma after the treatment for ALL is unclear. Diffuse lesion in all patients and gadolinium-enhanced lesion in Case 3 responded immediately after concomitant radiation and TMZ. Similarly, two patients survived without recurrence for 9 and 11 months after total resection, concomitant radiation and TMZ, and maintenance of TMZ [9]. To elucidate the effect of radiation therapy and TMZ to this entity, further accumulation of information is necessary in the future.

Conclusion

Radiation-induced glioblastoma after the treatment for ALL has unique clinical, radiological, histological, and molecular characteristics.

Compliance with ethical standards

Conflict of interest These authors declare that they have no conflict of interest.

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