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Successful Treatment of a CNS Tumor with BCOR Internal Tandem Duplication: A Case Report

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Abstract

A central nervous system (CNS) tumor with BCL-6 co-repressor (BCOR) internal tandem duplication (CNS tumor with BCOR ITD) is a rare tumor classified as an embryonal tumor by the World Health Organization classification (5th edition), and the prognosis is generally poor. A successfully treated case is reported, and its treatment is discussed. A five-year-old boy presented with a one-month history of headache and vomiting. Magnetic resonance imaging showed a well-demarcated, left-frontal tumor without perifocal edema. The patient underwent complete resection without a neurological deficit.

Anti-BCOR antibody showed strong immunoreactivity in tumor nuclei, and the tumor was diagnosed as a CNS tumor with BCOR ITD. The patient received craniospinal irradiation (CSI) comprising 23.4 Gy, followed by a boost to the primary site to a total dose of 30.6 Gy in daily fractions of 1.8 Gy.

The chemotherapy comprised four cycles of vincristine, cyclophosphamide, and cisplatin with peripheral blood stem cell rescue. The clinical course was uneventful throughout the treatment, the tumor has not recurred for four years, and no neurological impairment was reported. CSI and multiagent chemotherapy were effective for a CNS tumor with BCOR ITD.

Keywords: BCOR, embryonal tumor, craniospinal irradiation, multiagent chemotherapy, gross total resection

Introduction

A central nervous system (CNS) tumor with BCL-6 co-repressor (BCOR) internal tandem duplication (ITD) is a molecular entity classified by DNA methylation profiling in 2016 by Strum et al.[1)]. It is characterized by somatic ITD of BCOR in exon 15.[2)] This tumor was previously classified as CNS-PNET and was recently listed in the World Health Organization classification of CNS tumors.

Magnetic resonance imaging (MRI) of the tumor shows a well-circumscribed lesion, especially on fluid-attenuated inversion recovery and a hyper-intense mass on diffusion-weighted imaging (DWI) and variable enhancement with gadolinium.[3,4)]

Histologically, the tumor cells are oval to stellate and have oval nuclei with fine chromatins. They exhibit ependymoma-like perivascular pseudorosettes.[1)] Necrosis is often observed and commonly forms palisading.[5)]

The standard treatment has not been established, and patients are treated by various methods, such as temozolomide plus local radiotherapy or intensive multiagent chemotherapy with craniospinal irradiation. The clinical, radiological, pathological, and genomic features of the tumors remain unknown. The case of a five-year-old child is described, along with a discussion of the diagnosis and treatment of a CNS tumor with BCOR ITD.

Case Report

A five-year-old boy presented with a one-month history of headaches and vomiting and was admitted to our hospital. He had no neurological deficits, such as paresis and aphasia. MRI showed a well-demarcated, left-frontal tumor, which was partially enhanced by a gadolinium-based con-

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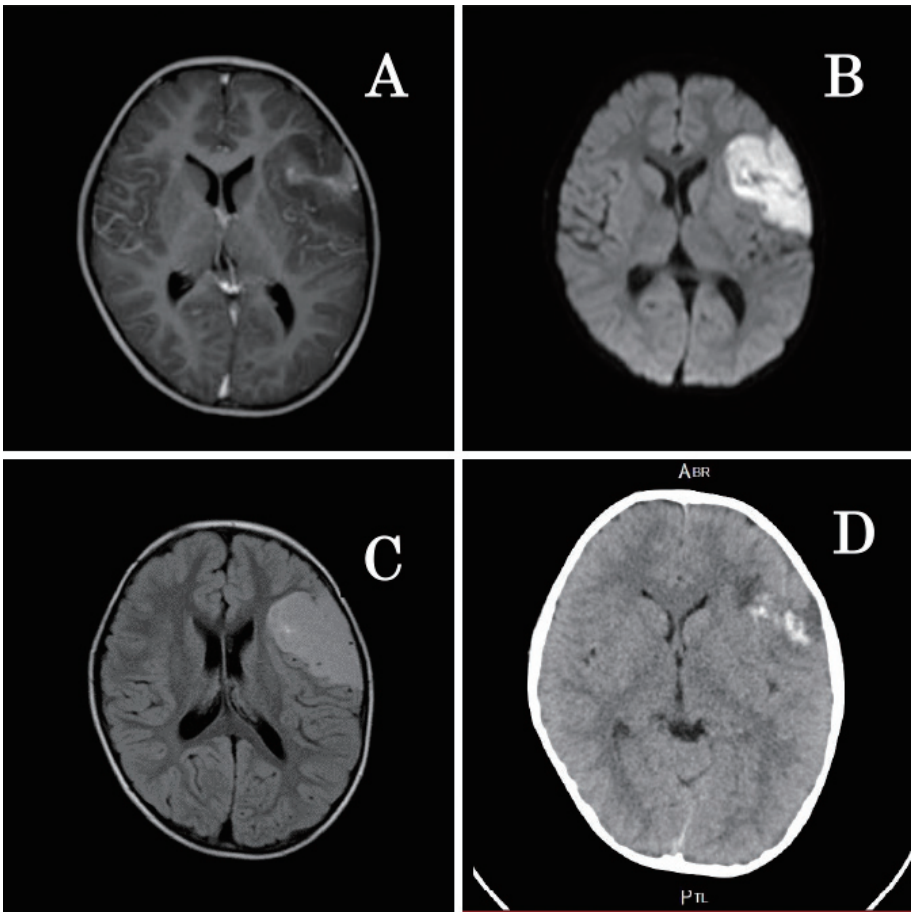

Fig. 1 Pre-operative image.
A: On MRI, a T1-weighted image shows a left frontal well-demarcated tumor, which was partially enhanced after gadolinium injection.
B: DWI of the tumor showed hyperintensity.
C: FLAIR shows the tumor is well-circumscribed.
D: CT revealed a minor bleeding or slight calcification.

trast agent (Fig. 1A-C). Diffusion-weighted imaging (DWI) of the tumor showed hyperintensity (Fig. 1B). Computed tomography showed partial high density, suggesting a minor bleeding or slight calcification (Fig. 1D).

The spinal cord dissemination was not found on MRI, and the cerebrospinal fluid cytology was negative. The patient underwent gross total resection by left frontotemporal craniotomy without any neurological deficit. No residual tumor was observed on postoperative MRI.

Hematoxylin-eosin (HE) staining of the tumor predominantly comprised compact spindle growth to oval cells with branching capillaries, which partly showed microcystic formation (Fig. 2A, B). Perivascular pseudorosettes with an anuclear fibrillary zone were present (Fig. 2C). The border between the tumor and normal brain parenchyma was relatively sharp. The tumor cells showed nuclear atypia at high magnification and clear eosinophilic cytoplasm. Mitotic counts were up to 6 per 10 high-power fields (Fig. 2D). The MIB-1 labeling index was high (28%) (Fig. 2E). Immunoreactivity for GFAP was absent in most tumor cells but focally present only in some tumor cells. Expressions of Olig2 (Fig. 2E) and S-100 protein (Fig. 2F) were diffusely observed. Immunopositivity for EMA was seen in scattered tumor cells. The tumor cells were negative for IDH-1 R132H.

Considering the possibility of a pediatric embryonal tumor, ITD was analyzed using immunostaining and PCR.

Anti-BCOR antibodies showed diffuse staining with strong immunoreactivity in tumor nuclei (Fig. 2G). PCR and direct sequencing assay identified the BCOR tandem duplication of exon 15. The 2-bp insertion (GT) and its upstream tandem duplication are shown in Fig. 3.

All other molecular gene alterations (IDH-1/2 mutation, H3F3A mutation, 1p/19q loss, MGMT methylation, RELA fusion mutation, and TERT promoter mutation (C228T)) were not observed.

After resecting the tumor, the patient received CSI comprising 23.4 Gy, followed by a boost to the primary site to

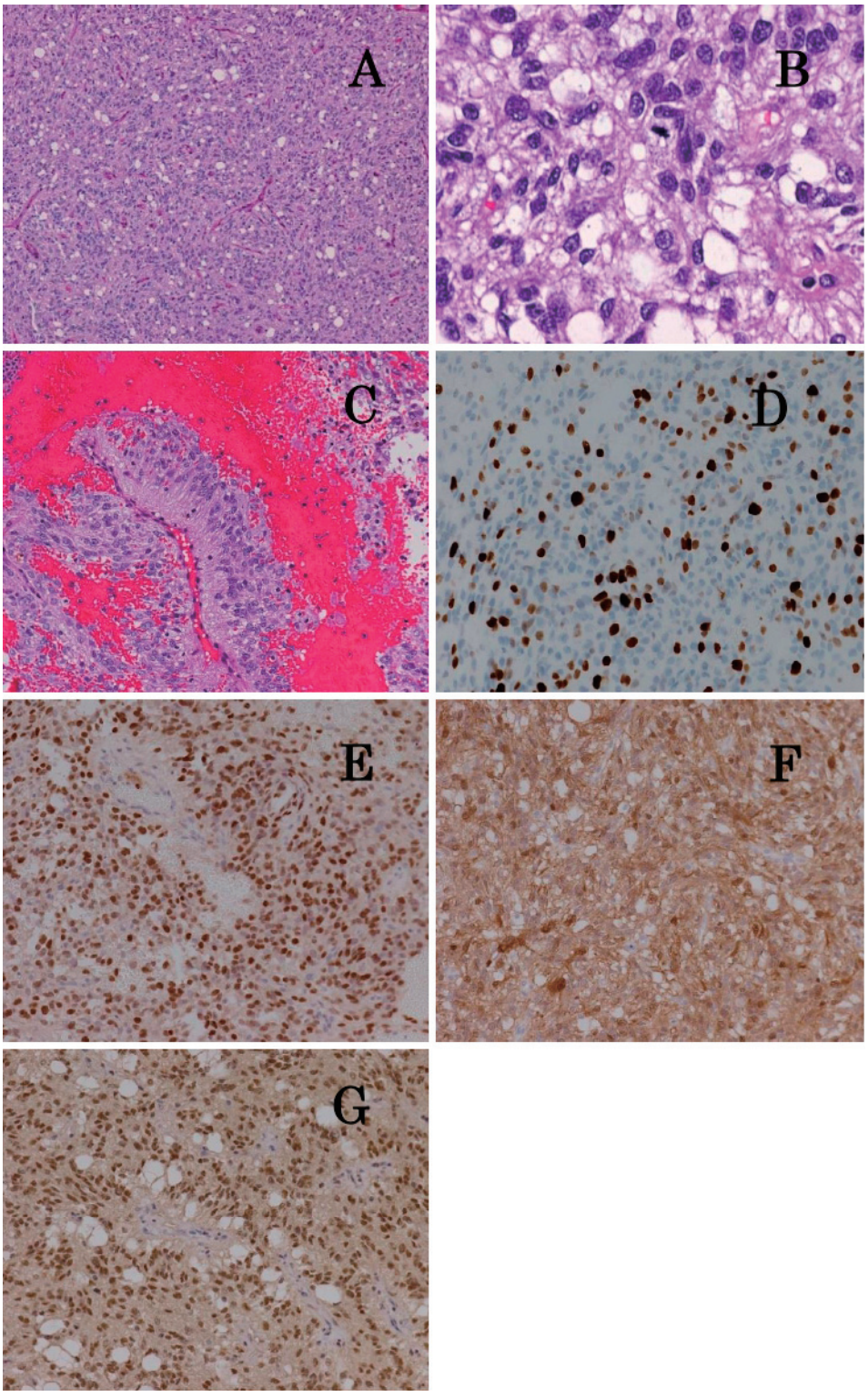

Fig. 2 A: HE staining of the tumor predominantly comprised compact spindle growth to oval cells with branching capillaries and partly showed microcystic formation. B: The tumor cells showed nuclear atypia at high magnification and clear eosinophilic cytoplasm. Mitotic counts were up to 6 per 10 high-power fields. C: Perivascular pseudorosettes with an anuclear fibrillary zone were present. D: The MIB-1 labeling index was high (28%). E: Expression of Olig2 was diffusely observed. F: Expression of S-100 protein was also diffusely observed. G: Anti-BCOR antibodies revealed diffuse, firmly in tumor nuclei.

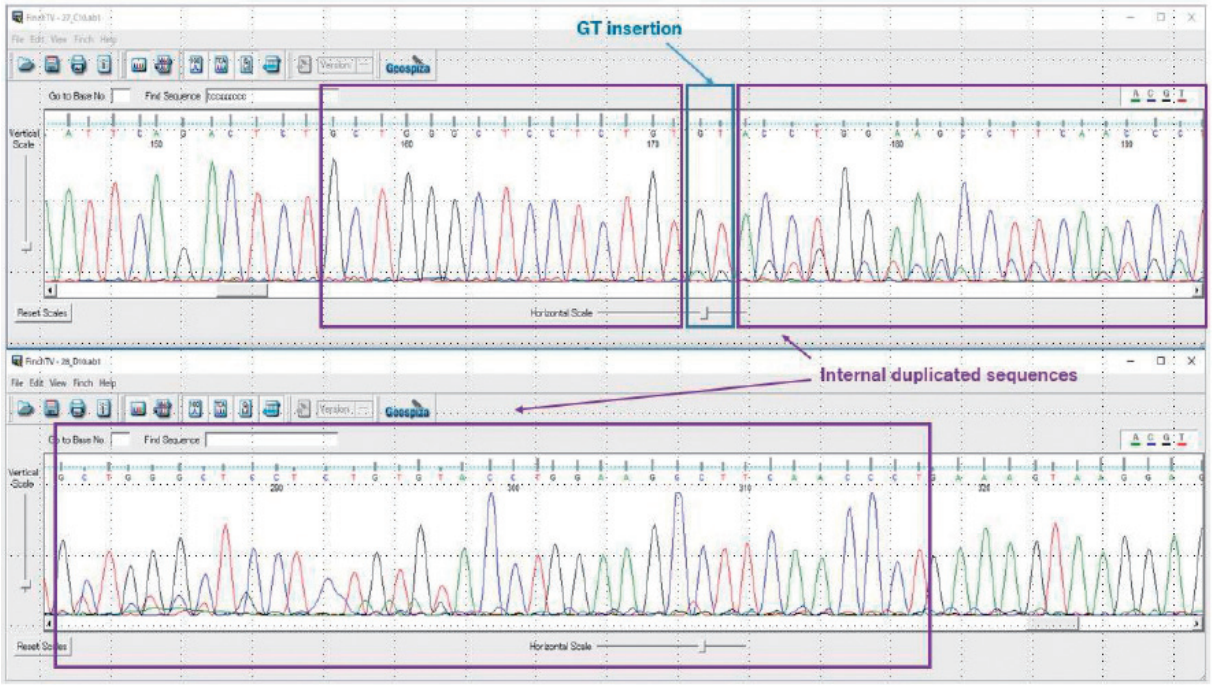

Fig. 3 BCOR exon 15 ITD by BCOR PCR assay.

a total dose of 54 Gy in daily fractions of 1.8 Gy.

The chemotherapy comprised four cycles of vincristine (1.5 mg/m^2), cyclophosphamide (2000 mg/m^2), and cisplatin (75 mg/m^2) with peripheral blood stem cell rescue.[6] The patient's clinical course was uneventful except for febrile neutropenia due to myelosuppression throughout the treatment, and there were no persistent complications.

The tumor has not recurred for more than four years after the treatment.

Discussion

Diagnosis of a CNS tumor with BCOR ITD

Although genetic analysis is necessary for diagnosing a CNS tumor with BCOR ITD, the MRI features are helpful in the first stage of diagnosis. Some reported cases had well-demarcated masses in the cerebral or cerebellar hemispheres.[1,3-5] Gardoen et al. reported that CNS tumor with BCOR ITD was relatively large masses with well-defined borders and no peritumoral edema.[4] This imaging feature can help in the differential diagnosis between CNS tumor with BCOR ITD and gliomas.

Since the present case showed a tumor with a sharp margin, glioma was not considered. BCOR ITD and gliomas should be included as diagnostic candidates.

Treatment

The treatment for a CNS tumor with BCOR ITD has not been standardized because of the rarity of the disease. Considering the previous classification as CNS-PNET, it had been treated as a high-grade glioma or embryonal tumor, such as medulloblastoma. For some patients, multiagent chemotherapy was administered for embryonal tumors, while for others, temozolomide was selected for high-grade gliomas (Table 1).

Patients treated with temozolomide have a higher tumor recurrence rate than patients treated with multiagent chemotherapy (75% (3/4) vs. 16.6% (2/12)) (Table 1).

Thus, we chose the treatment regimen of St. Jude Medulloblastoma-96 for high-risk medulloblastoma, which exhibited excellent outcomes.

Massimino et al. reported patients with CNS-PNET treated with adjuvant chemotherapy (methotrexate/etoposide/cyclophosphamide/carboplatin) and CSI with focal boost, followed by high-dose thiotepa with autologous stem cell rescue. For patients who could tolerate this complete schedule, the 5-year PFS and OS were 67% ± 11% and 61% ± 11%, respectively.[10]

Although clinical data are limited, most reported patients relapsed, and overall survival was poor.[2]

Regarding radiation therapy, four of seven cases (57%) of cranial irradiation showed recurrence, whereas none of the seven patients treated with CSI had recurrence during the observation period.

The cause of long-term disease control in the present case might be treatment with CSI and intensive multiagent chemotherapy.

Gross total resection is related to a good outcome.[11-13] Regina et al. reported that the 5-year OS of patients with CNS-PNET with GTR was 59% ± 11.4%, and those of non-

Table 1 Clinical features of the 25 patients of CNS tumor with BCOR ITD

Case No.	Age	sex	tumor lacation	Radio-therapy	initial chemotherapy	Time to Recurrence	Follow-up (yrs)	status at last follow up	surgery	Refer-ence
1	1	F	frontoparietal lobe	None	multiagent, platinum based	14 months	14.2	alive, NED	GTR	2
2	4	F	Cerebellum	CSI	multiagent, platinum based	(-)	1.8	alive, NED	GTR	2
3	3	F	Frontal lobe	Cranial	multiagent, platinum based	(-)	0.4	alive, NED	GTR	2
4	3	M	Cerebellum	None	None	4 months	2.3	alive with disease	GTR	2
5	2	F	Cerebellum	None	multiagent, platinum based	(-)	0.7	alive, NED	GTR	2
6	2	F	frontoparietal lobe	None	multiagent, platinum based	(-)	0.8	alive, NED	GTR	2
7	9	F	Basal ganglia	Cranial	TMZ & Bevacezumab	(-)	2.2	alive, NED	GTR	2
8	13	M	Frontal lobe	Cranial	TMZ & Bevacezumab	49 months	4.5	alive, NED	GTR	2
9	2	M	Cerebellum	Cranial	TMZ & Bevacezumab	31 months	2.9	alive, NED	GTR	2
10	12	M	frontoparietal lobe	CSI	multiagent, platinum based	(-)	1.1	alive, NED	GTR	2
11	5	M	Frontal lobe	Cranial	TMZ	12 months	unknown	alive with disease	unknown	3
12	6	M	Parietooccipital	Cranial	TMZ/VCR/CDDP/CCNU	unknown	unknown	alive with disease	GTR	7
13	3	M	Cerebellum	None	None	6 months	1.6	dead	GTR	1
14	4	M	Cerebellar hemisphere	None	VP16/carboplatin	6 months	1.8	dead	GTR	1
15	7	F	Cerebellar hemisphere	CSI	metronomic chemotherapy	(-)	1.2	alive, NED	GTR	1
16	11mo	M	Cerebellar hemisphere	None	None	(-)	0.2	dead	PR	3
17	6	M	Cerebellar hemisphere	Cranial	None	(+) unknown	unknown	unknown	GTR	3
18	6	M	temporal lobe	CSI	CDDP/CPM/VP16	(-)	3	dead	GTR	3
19	3	F	Cerebellar hemisphere	not available	Not available	unknown	Not available	Not available	GTR	3
20	7mo	M	Cerebellar hemisphere	None	None	(+) unknown	unknown	unknown	GTR	3
21	22	M	Cerebellopontine angle	None	CDDP/VP16	(-)	2 months	dead	PR	3
22	5	F	Frontal lobe	None	None	3 months	unknown	unknown	GTR	8
23	6	F	Cerebellar hemisphere. Cerebellopontine angle	CSI	carboplatin & etoposide	(-)	10 months	alive with NED	GTR	9
24	3	M	Cerebellar hemisphere	CSI	None	(-)	6 months	alive with NED	GTR	9
25	5	M	Cerebellar hemisphere	CSI R: CSI0/5 C4/6	VCR/CPM/CDDP recurrence: TMZ3/4 multi 2/10, CPM: cyclophospha-mide, TMZ: temozolomide, CDDP: cisplatin, VCR: vincristine	(-)	1.8	alive, NED	GTR GTR13/16	present case

NED: no evidence of disease, GTR: gross total resection, PR: partial resection

GTR were much worse (10% ± 7%).[12]

Due to the small number of cases, the relationship between patient prognosis and GTR/non-GTR is unclear. Thirteen of sixteen patients who received GTR survived, whereas all patients who had partial resection died early (Table 1). The gross total resection achieved in the present case might help the prognosis.

Conclusion

For well-defined intracranial tumors in children, a CNS tumor with BCOR ITD should be included in the differential diagnosis. CSI, intensive multiagent chemotherapy, and gross total resection may correlate to a good prognosis.

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Informed Consent

The consent from all the participants was obtained.

Conflicts of Interest Disclosure

The authors declare no financial or other conflicts of interest in relation to this case report and its publication.

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