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RESEARCH

Recurrence patterns and clinical outcomes in adult cerebellar glioblastoma

Sogo Oki[1] · Shigeru Yamaguchi[1] · Yukitomo Ishi[1] · Hiroaki Motegi[1,2] · Masayuki Gekka[1,3] · Zen-ichi Tanei[4] · Hiromi Kanno-Okada[5] · Emi Takakuwa[5] · Satoshi Tanaka[6] · Takashi Mori[7] · Kentaro Nishioka[8] · Hidefumi Aoyama[7] · Shinya Tanaka[4,5] · Miki Fujimura[1]

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Abstract

Background Cerebellar glioblastoma in adults is a rare brain tumor with poor outcomes. This study aimed to assess the clinical characteristics, genetic features, and prognosis of a series of cerebellar glioblastomas, with special attention to their recurrence patterns.

Methods We retrospectively analyzed patients who underwent treatment between 2008 and 2023. The patient characteristics, treatment methods, genetic features, and prognoses were assessed.

Results Among 274 cases of histological glioblastomas, eleven patients with cerebellar glioblastomas were identified. Pathological results revealed microvascular proliferation and/or necrosis in all cases. All patients underwent surgery and local radiotherapy combined with temozolomide chemotherapy. The median progression-free survival and overall survival were 15.3 months and 22.8 months, respectively. Subventricular zone involvement was recognized in ten patients. Of the eight patients who experienced recurrence, seven had distant or disseminated recurrence, and only one experienced local recurrence. None of the tumors harbored mutations in the *IDH1/2*, *H3F3A*, or *TERT* promoters. Three patients showed negative expression of O^6-methylguanine DNA methyltransferase (MGMT), and four patients showed positive expression.

Conclusions In our cohort, cerebellar glioblastomas showed clinical characteristics such as recurrence patterns and genetic features such as *IDH*, *H3F3A*, and *TERT* promoter regions that differed from those of typical supratentorial gliomas. Further studies are necessary to fully elucidate the clinical characteristics.

Keywords Glioblastoma · Cerebellum · Recurrence · Histological · GBM

Introduction

Glioblastomas represent the most frequent form of gliomas; however, their prevalence in the cerebellum is low (0.4–3.4%) [9, 27, 28]. Therefore, reports on the treatment, prognosis, and genetic information for this group of diseases are limited. Previous reports have described cerebellar glioblastomas as demonstrating a worse, better, or similar prognosis compared to supratentorial glioblastomas [1, 4, 5, 15, 19, 23, 32]. However, reports on recurrent patterns and genetic information are limited, with studies reporting this only in small groups of patients [12, 18]. The aim of this study was to further describe the clinical characteristics, including recurrent patterns and genetic features, of adult patients with cerebellar glioblastoma.

Methods

Study population

In this retrospective study, we included all adult patients (aged > 18 years) with a diagnosis of cerebellar glioblastoma based on imaging and pathological findings, treated at Hokkaido University Hospital between 2008 and 2023. Patient data, including clinical course, treatment outcome, radiological imaging findings, and pathological findings, were retrospectively analyzed by referring to their medical records. The lesions were identified using gadolinium-enhanced T1-weighted imaging. The tumor was classified as in contact with the subventricular zone (SVZ) if the tumor postcontrast enhancement adjoined the fourth ventricular ependyma (≧5 mm) [33]. The extent of tumor resection was defined as > 98% for gross total resection (GTR), 90–98%

Extended author information available on the last page of the article

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for subtotal resection (STR), 25–90% for partial resection (PR), and < 25% for biopsy by assessing residual tumor enhancement on magnetic resonance imaging within 48 h after surgery, as previously described [14, 37]. Patients with coexisting lesions in the supratentorial region or brainstem invasion at the initial presentation were excluded. Using pathological findings and genetic information, a certified neuropathologist made an integrated diagnosis based on the revised 5th edition (2021) of the WHO classification of central nervous system (CNS) tumors [20]. All manipulations were performed with the approval of our Institutional Review Boards (018–0363). The requirement for informed consent was waived, considering that this study was retrospective in nature. Progression-free survival (PFS) and overall survival (OS) were defined as the period between the date of the first surgery and either the first tumor recurrence on magnetic resonance imaging (MRI) or the patient's death from any cause and the date of death, respectively. OS after bevacizumab (Bev) treatment was calculated from the day Bev was first administered for recurrence to the day of tumor-related death.

We extracted adult patients with histological glioblastoma of the cerebrum from our institution's database from 2008 to 2023 and used them as a comparison group.

Genetic analysis and immunohistochemical analysis

DNA was extracted from frozen tumor tissues using the AllPrep DNA/RNA Mini Kit (Qiagen, Tokyo, Japan), in accordance with the manufacturer's recommendations. Mutation hotspots at codon 132 in *IDH1* and codon 172 in *IDH2*, the *TERT* promoter (C228T and C250T), and codons 27 and 34 of *H3F3A* were screened using Sanger sequencing, as previously described [13]. O^6-methylguanine DNA methyltransferase (MGMT) expression status was evaluated by immunohistochemical (IHC) analysis, as previously described [21].

Statistical analysis

Data were analyzed using JMP Pro (version 17.2.0; SAS Institute, Cary, NC) and GraphPad Prism (version 10.2.2; GraphPad Software, San Diego, CA). Fisher's exact test and Wilcoxon rank-sum test were applied for comparison between cerebellar and supratentorial glioblastomas groups. The Kaplan–Meier method was used for survival analysis with 95% confidence intervals. The log-rank test was used to compare the Kaplan–Meier curves.

Results

Patient demographics

A total of 274 patients were histologically diagnosed with glioblastoma between 2008 and 2023. Five patients harbored an *H3F3A* mutation and were diagnosed with "diffuse midline glioma," and were subsequently excluded. Four patients presented with coexisting lesions in the supratentorial region or brainstem invasion and were likewise excluded.

We identified 11 patients histologically diagnosed with cerebellar glioblastoma. All patients underwent surgical resection, with pathological findings and genetic information confirmed. A certified neuropathologist confirmed microvascular proliferation and/or necrosis in every case. Ultimately, we identified 11 patients diagnosed with "glioblastoma, *IDH* wildtype, CNS WHO grade 4." During the study period, 254 patients with supratentorial glioblastoma were treated at our institution.

Table 1 showed characteristics of 11 patients with cerebellar glioblastoma and 254 patients with supratentorial glioblastoma. No statistical significance was observed among each group in age at onset and sex. Conversely, some differences were observed between the two groups in

Table 1 Patient characteristics of adult cerebellar and supratentrial glioblastomas

		cerebellar glioblastomas ($N=11$)	supratentorial glioblastomas ($N=254$)	*P* values
Age	Mean	66.8 ± 9.8	65.1 ± 13.8	0.9679
Sex	Women/Men	5/6	103/151	0.7624
Preoperative KPS				0.0122
	≦70%	1	132	
	80–100%	10	122	
Extent of resection				0.0009
	GTR (> 98%)	8	81	
	STR (90–98%)	2	59	
	PR (25–90%)	1	46	
	Biopsy (< 25%)	0	68	

GTR gross total resection, *KPS* Karnofsky Performance Status, *PR* partial resection, *STR* subtotal resection

terms of preoperative Karnofsky performance status (KPS) and extent of tumor resection ($P = 0.0114$ and $P = 0.0009$, respectively).

Clinical characteristics of cerebellar glioblastoma

Table 2 summarizes the clinical and genetic features of cerebellar glioblastomas. The average age of cerebellar glioblastoma onset was 66.8 ± 9.8 years. The origin sites included the cerebellar hemispheres in six cases, vermis in one case, tonsil in one case, hemisphere to tonsil in one case, flocculus in one case, and cerebellar peduncle in one case. SVZ involvement was observed in ten patients (90.9%). All patients underwent surgery and chemoradiation therapy. Eight patients underwent GTR, two underwent STR, and one underwent PR. Radiotherapy consisted of localized irradiation of 60 Gy in 30 fractions (60 Gy/30 Fr) for nine patients, hypofractionated treatment of 40 Gy/15 Fr for one patient, and discontinuation of radiotherapy at 44 Gy/22 Fr for one patient due to a skin rash (case #5). Concurrent chemotherapy included temozolomide (TMZ) for all patients, though one patient discontinued treatment due to a drug rash (case #5). Adjuvant TMZ was continued according to the Stupp regimen [31]. Five patients were administered Bev at the time of recurrence, including one who also received a TMZ re-challenge. None of the 11 patients exhibited mutations in *IDH1/2*, *TERT* promoter, or *H3F3A*. Three patients showed negative expression of MGMT whereas four patients showed positive expression. Case #4 has been previously reported [35].

Recurrence pattern and treatment outcome of cerebellar glioblastoma

Eight of the 11 patients with cerebellar glioblastoma experienced recurrence during the observation period. Of these, one case (12.5%) involved local recurrence, while the remaining seven cases (87.5%) involved distant recurrence or dissemination, including spinal involvement in four cases. Contrastingly, in cases of supratentorial glioblastoma, recurrence was noted in 207 of 254 cases during the observation period. The recurrence pattern was local in 165 cases (79.7%) and distant recurrence or dissemination in 42 cases (20.3%). Distant recurrence or dissemination was significantly more common in cerebellar glioblastoma ($P = 0.0001$) (Fig. 1).

Figure 2 illustrates the Kaplan–Meier curves. The median PFS was 15.3 months. By the last follow-up, seven of the 11 patients had died. The median OS was 22.8 months (range: 5.8–165.9 months). The 1-, 2-, and 5-year survival rates were 80%, 45.7%, and 30.5%, respectively. In supratentorial glioblastoma, the median PFS was 8.6 months, and the median OS was 17.6 months. No significant differences were observed in PFS and OS between cerebellar and supratentorial glioblastomas ($P = 0.08$ and $P = 0.17$, respectively).

In the five cases of recurrent cerebellar glioblastoma treated with Bev, the median OS after Bev was 6.6 months (range 0.6–13.7 months). In the 104 patients with recurrent supratentorial glioblastoma, the median OS after Bev was 7.8 months. No significant difference was noted in OS after Bev treatment between the cerebellar and supratentorial glioblastomas ($P = 0.39$).

Illustrative case

Case #7 A 66-year-old male presented with a 1-week history of right-sided ataxia. MRI showed a mass with an enhanced wall in the right cerebellar hemisphere (Fig. 3A). Glioblastoma was suspected, and surgical resection via an occipital transtentorial approach was performed. Postoperative MRI showed successful tumor removal (Fig. 3B). Histopathological assessments revealed anaplastic cells with irregularly shaped nuclei and microvascular proliferation without necrosis (Fig. 3C). Immunostaining was negative for IDH1-R132H, and the patient was diagnosed with glioblastoma. Postoperative management consisted of conventional radiotherapy at 60 Gy/30 Fr along with TMZ. Twelve courses of adjuvant TMZ (150–200 mg/m^2, days 1–5, every four weeks) were administered. Five months later, the patient developed a walking disorder and right-sided hemiparesis. MRI showed an enhanced mass within the left corona radiata, with distant recurrence (Fig. 3D). After irradiation with 60 Gy/30 Fr and TMZ re-challenge, distant recurrent lesions disappeared. After six months, a recurrent lesion was observed in the cerebellar vermis (Fig. 3E), and Bev was administered. However, the patient succumbed to the disease 36.5 months following the initial treatment. Additional genetic analysis confirmed the presence of wildtype *IDH*, the *TERT* promoter, and *H3F3A*.

Case #8 A 68-year-old female presented with a 1-month history of nausea. MRI showed a round mass with an enhanced wall in the left cerebellar hemisphere (Fig. 4A). Glioblastoma was suspected, and surgical resection was conducted (Fig. 4B). The postoperative course was uneventful. Postoperative MRI showed successful tumor removal. Histopathological assessment revealed anaplastic cells with irregularly shaped proliferating nuclei, microvascular proliferation, and necrosis (Fig. 4C). Immunostaining was negative for IDH1-R132H, and the patient was diagnosed with glioblastoma. Postoperative management consisted of conventional radiotherapy at 60 Gy/30 Fr along with TMZ. Adjuvant TMZ (150–200 mg/m^2, days 1–5, every four weeks) was administered. On the fifth course, the patient experienced back pain and disseminated recurrence in the brain and spine (Fig. 4D, E). Subsequently, Bev was introduced; however, the patient

Table 2 Patient characteristics and results of adult cerebellar glioblastomas

Case No	Age/sex	Primary lesion	SVZ involvement	Surgical resection	Post-operative treatment	PFS (months)	Pattern of progression	Treatment at recurence	OS (months)	OS after Bev (months)	Status	IDH mutation type	TERT promoter status	H3F3A status	MGMT expression
1	60/F	tonsil	yes	GTR	Radiation (60 Gy/30Fr) TMZ	16.3	Dissemination (supratentorial)	no	20.8	-	dead	wild	wild	wild	NA
2	61/F	vermis	yes	GTR	Radiation (60 Gy/30Fr) TMZ	165.9	-	-	165.9	-	dead	wild	wild	wild	NA
3	55/F	tonsil + hemisphere	yes	STR	Radiation (60 Gy/30Fr) TMZ	15.3	Local	no	23.7	-	NA	wild	wild	wild	positive
4	70/M	hemisphere	yes	GTR	Radiation (60 Gy/30Fr) TMZ	6	Distant (thoracic vertebra)	Radiation	11	-	dead	wild	wild	wild	negative
5	79/M	hemisphere	yes	GTR	Radiation (44 Gy/22Fr)* TMZ	14	Dissemination (supra + infratentorial)	Bev	22.8	8.4	dead	wild	wild	wild	negative
6	84/M	hemisphere	no	GTR	Radiation (40 Gy/15Fr) TMZ	-	-	-	46.9	-	alive	wild	NA	NA	NA
7	66/M	hemisphere	yes	GTR	Radiation (60 Gy/30Fr) TMZ	20.3	Dissemination (supra + infratentorial)	TMZ rechallenge Radiation Bev	36.5	4.7	dead	wild	wild	wild	NA
8	68/F	hemisphere	yes	GTR	Radiation (60 Gy/30Fr) TMZ	8.2	Dissemination (supratentorial + spinal cord)	Bev	11.4	3.1	dead	wild	wild	wild	positive
9	71/M	flocculus	yes	STR	Radiation (60 Gy/30Fr) TMZ	-	-	-	6.8	-	alive	wild	wild	wild	negative
10	70/F	hemisphere	yes	GTR	Radiation (60 Gy/30Fr) TMZ	2	Dissemination (supratentorial + spinal cord)	Bev	16	13.7	dead	wild	wild	wild	positive
11	51/M	cerebellar peduncle	yes	PR	Radiation (60 Gy/30Fr) TMZ	11.6	Dissemination (spinal cord)	Bev	13	0.6	alive	wild	wild	wild	positive

Bev Bevacizumab, *CNS* central nervous system, *Fr* fractions, *GTR* gross total removal, *Gy* gray, *IDH* isocitrate dehydrogenase, *MGMT* O^6-methylguanine DNA methyltransferase, *NA* not appricable, *OS* overall survival, *PFS* progression free survival, *PR* partial resection, *STR* subtotal resection, *SVZ* subventriclar zonne, *TERT* telomerase reverse transcriptase, *TMZ* temozolomide, *WHO*: world health organization, * interruption

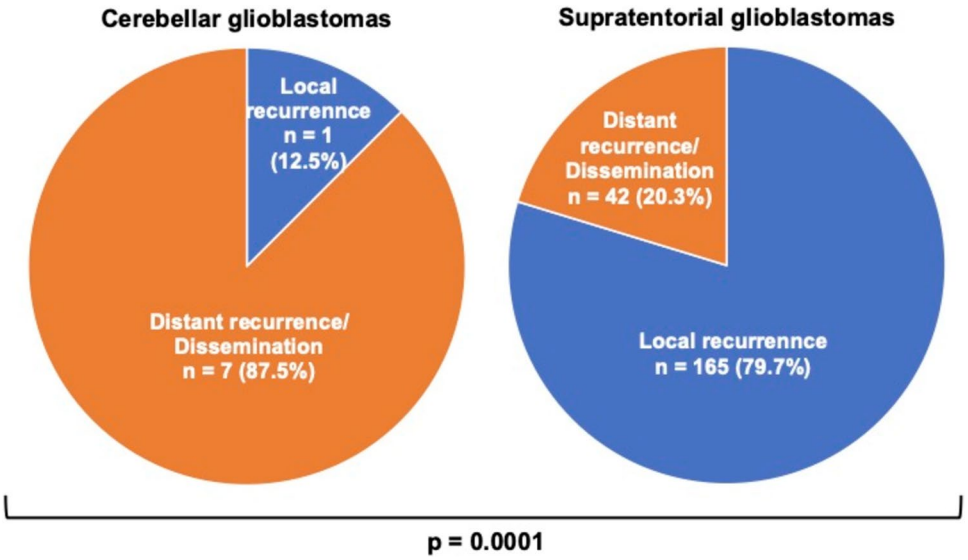

Fig. 1 Recurrence patterns of cerebellar and supratentorial glioblastomas. Distant recurrence or dissemination was significantly more common in cerebellar glioblastomas ($P=0.0001$)

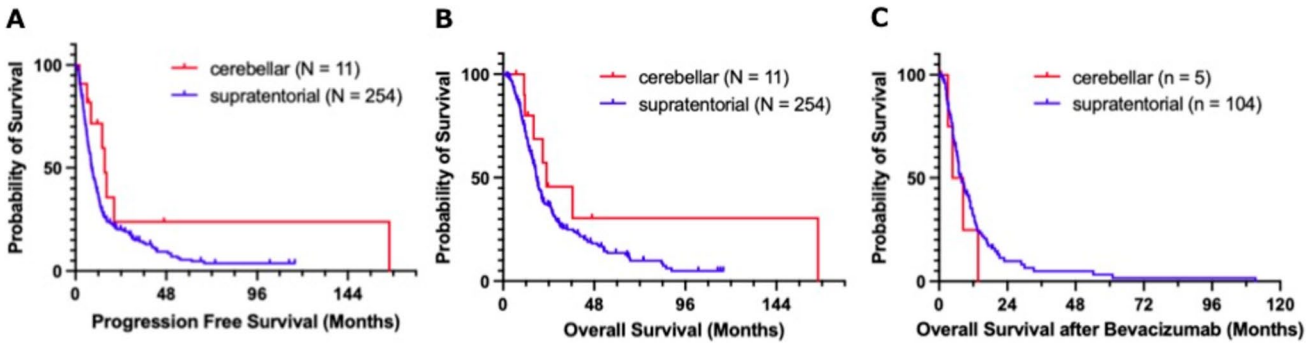

Fig. 2 Kaplan–Meier survival curve for cerebellar glioblastomas in this study. No differences were noted in progression-free survival **A**, overall survival **B**, and overall survival after bevacizumab (**C**) between cerebellar and supratentorial glioblastomas ($P=0.08$, $P=0.17$, and $P=0.39$, respectively)

succumbed to the disease 11.4 months following the initial treatment. Additional genetic analysis confirmed the presence of wildtype *IDH*, the *TERT* promoter, and *H3F3A*.

Discussion

Only a limited number of reports on cerebellar glioblastoma exist, owing to its rarity. Recently, multiple reports on prognostic data have emerged [1, 4–6, 12, 15, 19, 23, 32, 36]. However, several unknown aspects of its clinical and genetic characteristics still remain. In this retrospective study, we analyzed cases of cerebellar glioblastoma in accordance with the WHO 2021 criteria [20]. We found several important aspects of cerebellar glioblastoma.

First, recurrent cerebellar glioblastoma is characterized by a high rate of distant metastasis and meningeal dissemination, which differs from that of supratentorial glioblastoma. Generally, most recurrent patterns have been reported as local recurrences (79.3–80%), with distant recurrences being limited (10.3–20%) in glioblastomas [7, 24]. In our series of cerebellar glioblastomas, seven of the eight cases (87.5%) that recurred were distant or disseminated recurrences, and four of these cases involved the spinal region. Few reports exist on the recurrence patterns of cerebellar glioblastomas. Akimoto et al. reported disseminated recurrence in two cerebellar glioblastoma cases [2]. Additionally, Picart et al. reported that more than half of recurrence cases in cerebellar glioblastoma were distant or meningeal recurrences [23]. We believe that this difference in relapse patterns is of great clinical importance. Glioblastoma has an extremely high recurrence rate; therefore, it is essential to consider factors beyond local recurrence during follow-up. The high incidence of distant and disseminated recurrences may be associated with the anatomical location. Medulloblastoma, which shares the same CNS WHO grade 4 as

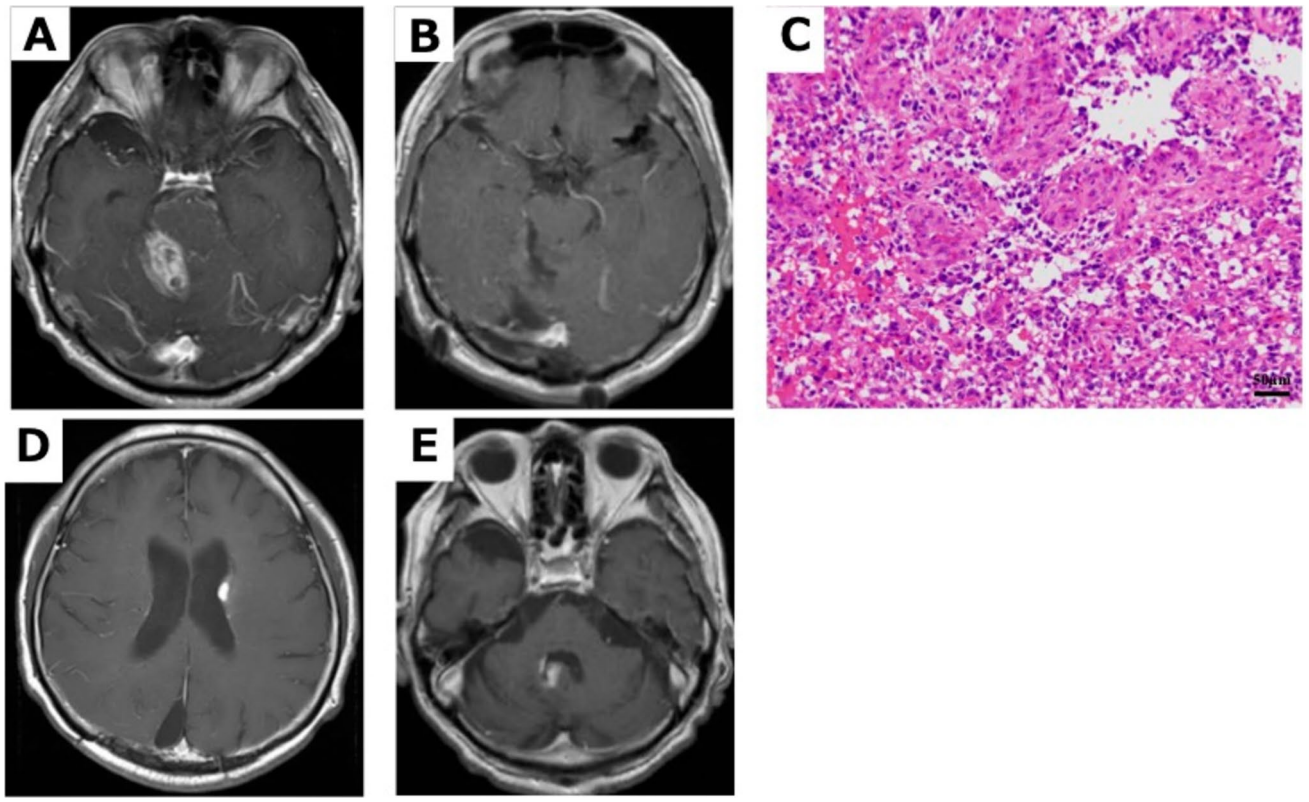

Fig. 3 Radiological findings of case #7. **A** Gadolinium-enhanced T1-weighted imaging (Gd-T1WI) reveals an enhanced lesion in the right cerebellar hemisphere. **B** Gd-TIWI reveals no residual tumor following surgery. **C** Hematoxylin and eosin staining shows anaplastic tumor cells with a high nuclear-to-cytoplasmic ratio, proliferating with microvascular proliferation (×200). **D**, **E** Gd-T1WI reveals enhanced lesions along the left lateral ventricle and fourth ventricle walls

glioblastoma and occurs in the posterior fossa, demonstrates a high rate (58–78%) of distant recurrence [10, 11]. Additionally, leptomeningeal relapse has been reported to often occur (33–50%) in metastatic brain tumors in the posterior fossa [3, 29, 34]. As malignant tumors in the posterior fossa often recur distantly or spread, cerebellar glioblastomas likely demonstrate similar tendencies. Furthermore, in our cerebellar glioblastomas, we observed SVZ involvement at a high frequency (90.9%). SVZ involvement has been reported as a risk factor for distant recurrence and dissemination in supratentorial glioblastomas [33]. The cerebellum, which is smaller in volume compared to the cerebrum and has anatomical characteristics that make it closely adjacent to the ventricular system, may be associated with the characteristic recurrence patterns. Moreover, the high extent of resection achieved in our cerebellar glioblastoma cases may have contributed to the reduced incidence of local recurrence.

Second, differences exist in genetic features. In glioblastomas, *TERT* promoter mutations have been reported to occur in approximately 80% of cases [8, 16]. In the present study, the *TERT* promoter was wildtype in all cases. Only a few reports exist on the genetics of cerebellar glioblastoma. One prior study reported that *TERT* promoter mutations occur in only one of four cases of cerebellar glioblastoma, *IDH*-wildtype [12]. Another reported this alteration in two of 19 cases of cerebellar glioblastoma [6]. Reinhardt et al. reported that *TERT* promoter mutations were observed in 31% (9/29) of cerebellar glioblastomas, in contrast to 77% (98/127) of supratentorial glioblastomas [25]. They used DNA methylation profiles to clarify the differences between cerebellar and supratentorial glioblastoma. *IDH* wildtype glioblastoma can be classified into seven DNA methylation subgroups. Among these, "glioblastoma *IDH* wildtype midline (GBM MID)" exhibits a low *TERT* promoter mutation rate (8%), whereas "glioblastoma *IDH* wildtype subclass mesenchymal (GBM MES)", "glioblastoma *IDH* wildtype subclass RTK I (GBM RTK I)" and "glioblastoma *IDH* wildtype subclass RTK II (GBM RTK II)" show higher *TERT* promoter mutation rates (78%, 77%, and 83%, respectively) [30]. Cerebellar glioblastomas are characterized by a higher prevalence of GBM MID and a lower frequency of GBM MES and GBM RTK II [25]. This distribution likely accounts for the lower incidence of *TERT* promoter mutations in cerebellar glioblastoma. These findings suggest that glioblastomas arising in the cerebellum and supratentorial regions exhibit distinct genetic profiles. Nomura et al. reported that diffuse

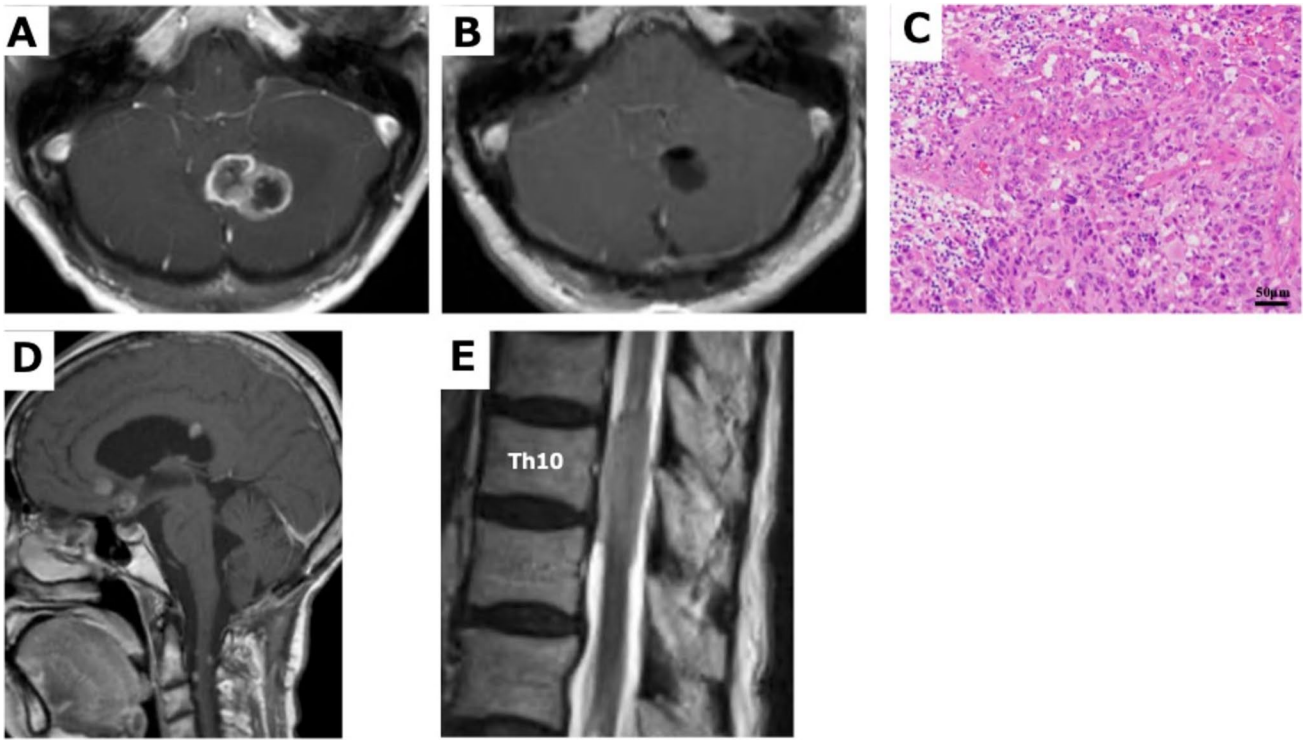

Fig. 4 Radiological findings of case #8. **A** Gadolinium-enhanced T1-weighted imaging (Gd-T1WI) shows ring-like enhancement in the left cerebellar hemisphere. **B** Gd-TIWI indicates no residual tumor following surgery. **C** Hematoxylin and eosin staining reveals pleomorphic tumor cells with irregular-shaped nuclei and eosinophilic cytoplasm, proliferating with microvascular proliferation (×200). **D** Gd-T1WI shows multiple enhanced lesions in the supratentorial and spinal areas. **E** T2-weighted imaging reveals an iso-intense mass within the spinal canal at the Th 10 level

cerebellar gliomas had characteristics genetic alteration and epigenetic profiles compared to most cerebral gliomas, which included frequent *SETD2* and *PPM1D* alteration and *PDGFRA*-related genetic and epigenetic signatures. They posit that variations in the cellular origins of tumors arising from distinct brain regions significantly contribute to the observed outcomes. These variations in molecular profiles may likewise contribute to the differential incidence of glioblastoma in the cerebellum versus the cerebrum.

Third, the prognosis of cerebellar glioblastomas is similar to that of supratentorial glioblastomas. Several previous reports exist on cerebellar glioblastoma [1, 4–6, 12, 15, 19, 23, 32, 36]. Among these, cerebellar glioblastoma prognosis has been reported to be poor, good, or similar to that of supratentorial glioblastoma [1, 4–6, 15, 19, 23, 32]. However, most reports include a mixture of different subgroups, such as those diagnosed solely based on pathological results without *IDH* status or those containing H3K27M mutations. *IDH* and H3K27M mutations are factors associated with survival prognosis [23, 31]. This report is based exclusively on the WHO 2021 diagnostic criteria for cerebellar glioblastoma. Compared to supratentorial glioblastoma at the same time, OS and PFS were similar. Cerebellar glioblastoma has a high proportion of GBM MID with low frequency of *TERT* mutations, and this GBM MID has a slightly better prognosis than other glioblastomas with high frequency of *TERT* mutations [25, 26]. In our cohort, the cerebellar gliomas had favorable prognostic factors such as resection rate [17]. These results suggest that there may be no difference in prognosis between supratentorial and cerebellar glioblastomas, despite differences in recurrence patterns. Contrastingly, the median OS following Bev therapy was 6.6 months, although distant metastasis and meningeal dissemination are common recurrence forms. No significant difference was observed compared to supratentorial glioblastoma. The only report on the treatment outcomes of Bev for recurrent cerebellar glioblastoma is a case report. Linsenmann et al. reported achieving 12 months of control by administering Bev and radiation therapy for spinal metastases of cerebellar glioblastoma [18]. Based on these findings, Bev's effectiveness for distant and disseminated recurrence of cerebellar glioblastoma may be similar to that of supratentorial glioblastoma.

At our facility, we treat cerebellar glioblastoma in the same manner as supratentorial glioblastoma. We conducted surgical resection followed by adjuvant treatment consisting of TMZ radiochemotherapy as per the Stupp regimen [31]. Based on the treatment findings, treatment according to supratentorial glioblastoma can be considered reasonable

at present. Nevertheless, given the various recurrence patterns, we propose that a follow-up MRI should encompass an examination of the spine and spinal cord in addition to the brain.

Limitations

This retrospective analysis has some limitations, including a small sample size and a single-center design. Additionally, a search for *EGFR* amplification and alterations in chromosome 7 and 10 copy numbers has not been possible, and DNA methylation analysis was not performed. Since histologically classified cerebellar glioblastomas are sometimes molecularly classified as anaplastic astrocytoma with piloid features [25], it is possible that this cohort included cases of this subtype. Larger cohorts are required to elucidate the clinical and genetic features of cerebellar glioblastomas. Furthermore, a possibility of selection bias exists in defining the cohort by tumor type, which can be confirmed by pathological and genetic information obtained via surgical resection. Thus, the study likely did not include patients with poor prognosis who were not eligible for surgery. Thus, prospective trials are necessary to demonstrate the implications of these findings.

Conclusion

Here, we report the clinical and genetic features of cerebellar glioblastoma. Although several cases of distant and disseminated recurrence were observed, the prognosis was similar to that of supratentorial glioblastoma. *TERT* promoter mutations were not noted in any case, suggesting variations in genetic characteristics. Further assessment and a better understanding of the clinical and genetic features of this disease are necessary to establish more effective treatments.

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Data availability No datasets were generated or analysed during the current study.

Code availability Not applicable.

Declarations

Consent for publication The authors declare their consent for publication.

Consent to participate Since the study was retrospective, the requirement for informed consent was waived.

Ethical standards All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Conflicts of interest The authors declare no competing interests.

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Authors and Affiliations

Sogo Oki[1] · Shigeru Yamaguchi[1] · Yukitomo Ishi[1] · Hiroaki Motegi[1,2] · Masayuki Gekka[1,3] · Zen-ichi Tanei[4] · Hiromi Kanno-Okada[5] · Emi Takakuwa[5] · Satoshi Tanaka[6] · Takashi Mori[7] · Kentaro Nishioka[8] · Hidefumi Aoyama[7] · Shinya Tanaka[4,5] · Miki Fujimura[1]

✉ Shigeru Yamaguchi
yama-shu@med.hokudai.ac.jp

Sogo Oki
will.you.clear.up.tomorrow@gmail.com

Yukitomo Ishi
ishi-y@huhp.hokudai.ac.jp

Hiroaki Motegi
moccihiro@gmail.com

Masayuki Gekka
gekka0921@gmail.com

Zen-ichi Tanei
tanei@med.hokudai.ac.jp

Hiromi Kanno-Okada
kanno-kanno@med.hokudai.ac.jp

Emi Takakuwa
emitaka@huhp.hokudai.ac.jp

Satoshi Tanaka
binntanaka@med.hokudai.ac.jp

Takashi Mori
tamori-tym@umin.ac.jp

Kentaro Nishioka
k.nishioka@pop.med.hokudai.ac.jp

Hidefumi Aoyama
h-aoyama2019@med.hokudai.ac.jp

Shinya Tanaka
tanaka@med.hokudai.ac.jp

Miki Fujimura
fujimur@med.hokudai.ac.jp

[1] Department of Neurosurgery, Hokkaido University Graduate School of Medicine, Kita 15 Nishi 7, Kita-Ku, Sapporo, Hokkaido, Japan

[2] Department of Neurosurgery, Sapporo Azabu Neurosurgical Hospital, Sapporo, Japan

[3] Department of Neurosurgery, Tomakomai City Hospital, Tomakomai, Japan

[4] Department of Cancer Pathology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

[5] Department of Surgical Pathology, Hokkaido University Hospital, Sapporo, Japan

[6] Center for Cause of Death Investigation, Faculty of Medicine, Hokkaido University, Sapporo, Japan

[7] Department of Radiation Oncology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

[8] Global Center for Biomedical Science and Engineering, Faculty of Medicine, Hokkaido University, Sapporo, Japan