Clinical characteristics and pathogenesis of cerebellar glioblastoma

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Abstract. Cerebellar glioblastomas (GBMs) are rare, with neither their pathogenesis nor prognosis being completely understood. The present study aimed to clarify the clinical characteristics of cerebellar GBMs by comparison with supratentorial GBMs, focusing particularly on the pathogenesis. The clinical factors between cerebellar (n=10) and supratentorial (n=216) GBMs were compared. Additionally, p53 and epidermal growth factor receptor (EGFR) levels were investigated in six patients by immunostaining as well as the isocitrate dehydrogenase 1 (IDH1) status of five patients by direct sequencing. Eight males and two females participated in the present study, the mean age at diagnosis was 56.6 years and the range 37-75 years. Four patients presented with hydrocephalus and one with brainstem involvement, and two patients were diagnosed with neurofibromatosis type 1. Two patients had previously received radiotherapy, eight patients received postoperative radiotherapy and seven chemotherapy. The mean Karnofsky performance status (KPS) score was lower in patients with cerebellar GBMs compared to those with supratentorial GBM; however, the survival times did not differ between the two groups. All of the cases of six cerebellar GBMs were p53-positive and EGFR-negative, as detected by immunostaining, consistent with secondary GBM. However, no IDH1 mutations were detected in any of the five cases of cerebellar GBMs analyzed, indicating that these tumors were not of the secondary type. The KPS score with cerebellar GBMs may be lower due to hydrocephalus, which was ameliorated by surgery but may have impacted the survival rate. It was confirmed that cerebellar GBMs were identical to supratentorial GBMs with respect to its clinical features, with the possible exception of the KPS score. The present study's genetic analyses indicated that cerebellar GBMs may develop via a pathway different from that of either primary or secondary GBM.

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Introduction

Glioblastoma (GBM) is the most common type of malignant brain tumor. However, cerebellar GBMs are rare and accounts for 0.4-3.4% of all GBM cases (1-3). Cerebellar GBMs are not yet completely understood in terms of prognosis, due to their rarity. The present study aimed to clarify the clinical characteristics of cerebellar GBMs by comparison with supratentorial GBMs. GBMs may develop *de novo* (primary type) or from previous low grade astrocytomas (secondary type) (4,5). Secondary GBMs often contain a p53 mutation (65%), while primary GBMs are generally characterized by the absence of heterozygosity 10q, epidermal growth factor (EGFR) amplification (36%) and p53 mutation at a frequency lower than 30% (5). The isocitrate dehydrogenase 1 (IDH1) mutation may be highly a selective molecular marker for secondary GBMs that complement clinical criteria to distinguish them from primary GBMs (6). Furthermore, the present study aimed to focus on the pathogenesis of cerebellar GBMs.

Materials and methods

Cerebellar GBMs (n=10) were compared with supratentorial (n=216) GBMs with respect to clinical factors [gender, age, Karnofsky performance status (KPS) score, extent of surgical resection and survival time]. In addition, p53 and EGFR levels were investigated in six patients by immunostaining and the IDH1 status of five patients by direct sequencing. The present study was approved by the ethics committee of Kumamoto University Hospital, Kumamoto, Japan). Written informed consent was obtained from the patients and/or their legal guardians.

Immunostaining. Surgical specimens were fixed, embedded in paraffin and 4-μm sections were prepared. The sections were deparaffinized in xylene and rehydrated in a graded ethanol-to-water series. Endogeneous peroxidase activity was blocked with hydrogen peroxidase. Immunostaining was performed using the avidin-biotinylated enzyme

Table I. Clinical characteristics of glioblastomas in the cerebellum and in the cerebral hemisphere.

Factors	Characteristics	Cerebellar	Cerebral	P-value
Cases (n)		10	226	
Gender	Male	8	134	NS
	Female	2	92	
Mean age (years)		56.6	58.1	NS
Mean KPS		68.0	80.4	0.03
Surgery	Total	2	89	NS
	Partial or biopsy	8	137	
Median survival (months)		9	12	NS

KPS, Karnofsky performance status. NS, not significant.

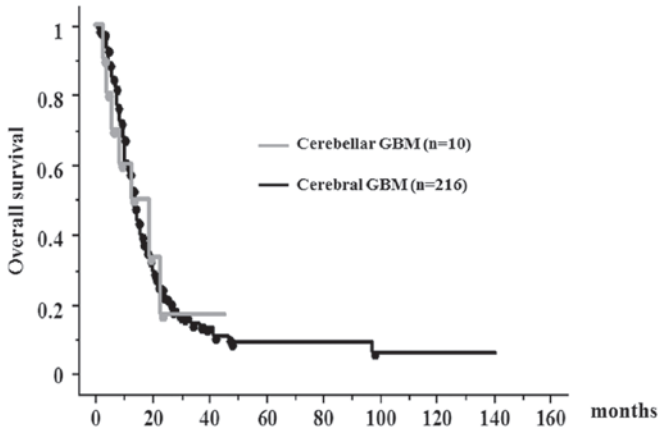

Figure 1. No significant difference in the survival time between cerebellar and supratentorial GBM patients was identified. GBM, glioblastomas.

complex (ABC) method (VECTASTAIN ABC kit; Vector Laboratories, Burlingame, CA, USA). The following primary antibodies were used: Anti-glial fibrillary acidic protein (GFAP; Dako, Tokyo, Japan), anti-MIB-1 (Dako), anti-p53 (Do-7, Dako) and anti-EGFR (EGFR113; Novocastra Laboratories Ltd., Milton Keynes, UK).

Direct DNA sequencing of IDH1 mutations. Genomic DNA was isolated from the surgical specimens using the Qiagen DNA Mini kit (Qiagen, Valencia, CA, USA). The polymerase chain reaction (PCR) primers for the genomic region corresponding to the IDH1 exon 4 that encodes the codon R132 were as follows: IDH1 sense, 5'-AAACAAATGTGGAAATCACC-3' and antisense, 5'-TGCCAACATGACTTACTTGA-3'. The PCR conditions were: 94˚C for 5 min, 36 cycles at 94˚C for 30 sec, 55˚C for 30 sec and 72˚C for 1 min, followed by an extension at 72˚C for 5 min. PCR was performed using Ex-Taq high-sensitivity DNA polymerase (Takara Bio, Shiga, Japan). The PCR products were purified using the QIAquick PCR purification kit (Qiagen Valencia, CA, USA) according to the manufacturer's instructions. Sequencing reactions were performed using the primers mentioned above and a Big Dye Terminator Cycle Sequencing kit (PE Applied Biosystems, Foster City, CA, USA) on an ABI377 automated sequencer (PE Applied Biosystems).

Summary of cases. The characteristics of the patients with cerebellar GBMs are described in Table I. There was no clinical or histological evidence of a pre-existing, less malignant precursor lesion in all of the cases. Of the 10 patients, six (patients 1, 2, 3, 4, 5, 6) were treated at Kumamoto University Hospital between 1997 and 2010. During this time, 216 patients with supratentorial GBMs were also treated. In this series of eight males and two females, the mean age at diagnosis was 56.6 years and the range was 37-75 years. The average KPS score was 68.0. A total of four patients suffered from hydrocephalus, one had brainstem involvement and two patients had neurofibromatosis type 1. Two patients had previously received radiotherapy, one for a medulloblastoma 34 years earlier, and the other for a hemangioblastoma 15 years earlier. Two patients underwent macroscopic total resection, the other eight partial resection and eight patients received postoperative radiotherapy and seven chemotherapy. In total, seven patients died at 3, 4, 6, 9, 13, 19 and 23 months, respectively, following surgical resection. Three patients were alive as of August 2011.

Results

Clinical characteristics and survival times of cerebellar GBM patients. Only the mean KPS score was lower in patients with cerebellar GBMs compared to those with supratentorial GBMs (Table I). No significant difference was noted in survival time between the cerebellar and supratentorial GBM patients (Fig. 1).

p53 and EGFR immunostaining and IDH1 status in cerebellar GBMs. All of the six cerebellar GBMs were p53-positive and EGFR-negative by immunostaining. Additionally, no IDH1 mutations were detected in any of the five cerebellar GBMs analyzed (Table II).

Illustrative patient

Patient six. In April 2010, a 45-year-old man presented with nausea, vomiting and gait disturbance. The patient had been diagnosed with neurofibromatosis type 1 by a dermatologist five years earlier. A neurological examination revealed cerebellar ataxia and magnetic resonance (MR) imaging revealed a 35 mm in diameter tumor in the cerebellar vermis. The tumor had relatively defined borders, demonstrated mild peritumoral edema and was heterogeneously enhanced with gadolinium

Table II. Clinical data of 10 patients with cerebellar glioblastoma.

Case	Age (years)	Gender	Location	Hydrocephalus	Brain stem invasion	Surgery	IDH1	Survival (months)	Other Findings
1	51	F	Rt hemisphere	(-)	(-)	partial	wild	23	
2	75	M	Lt hemisphere, vermis	(+)	(-)	partial	wild	9	
3	41	M	Lt hemisphere, vermis	(+)	(-)	partial	wild	6	radiation induced
4	50	M	Rt hemisphere, vermis	(+)	(-)	partial	not investigated	alive	NF-1
5	60	M	Rt hemisphere	(-)	(-)	partial	wild	alive	
6	45	M	vermis	(-)	(-)	total	wild	alive	NF-1
7	71	M	vermis	(+)	(+)	partial	not investigated	3	
8	37	M	vermis	(-)	(-)	partial	not investigated	4	radiation induced
9	68	F	Lt hemisphere	(-)	(-)	total	not investigated	19	
10	68	M	Rt hemisphere, vermis	(-)	(-)	partial	not investigated	13	

Rt, right; Lt, left; IDH, isocitrate dehydrogenase; NF-1, neurofibromatosis type1; M, male; F, female.

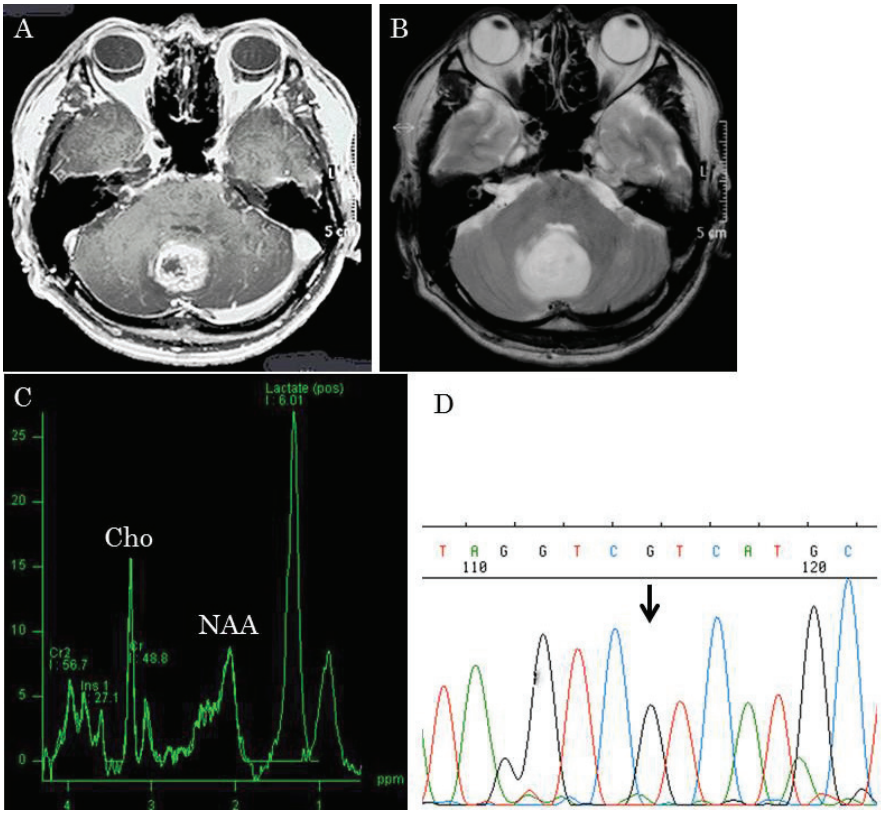

Figure 2. (A) T1-weighted magnetic resonance (MR) imaging with Gd-DTPA revealed a heterogeneously enhanced lesion in the cerebellar vermis. (B) T2-weighted MR imaging demonstrated that the mass had relatively defined borders with mild peritumoral edema. (C) MR spectroscopy of the lesion demonstrated a high choline peak in contrast to the decreased *N*-acetyl-aspartate peak observed with high-grade tumors. (D) The wild-type of the IDH1 gene was detected by direct sequencing. (Arrow indicates codon 132). Gd-DTPA, gadolinium diethylene triamine pentaacetic acid; MR, magnetic resonance.

(Fig. 2A and B). MR spectroscopy of the lesion demonstrated a high choline peak in contrast to a decreased *N*-acetyl-aspartate peak (Fig. 2C). A total tumor resection via a suboccipital craniotomy was performed. A histological examination revealed GBM. Tumor cells were spindle-shaped with irregular, moderately pleomorphic nuclei (Fig. 3A and B). The tumor cell cytoplasm was positive for GFAP (Fig. 3C) and ~20% of the cell nuclei were positive for the MIB1 gene (Fig. 3D). The

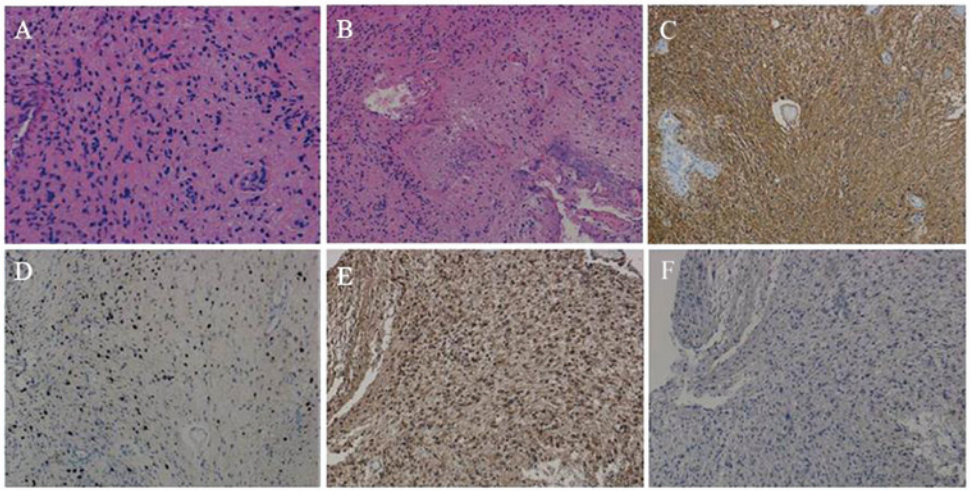

Figure 3. (A) Histological examination of the excised specimens revealed a cellular tumor composed of spindle-shaped cells with irregular, moderately pleomorphic nuclei (H&E staining). (B) Pseudo-palisading necrosis was present (H&E staining). (C) The tumor cells revealed cytoplasmic positivity for glial fibrillary acidic protein. (D) In total, ~20% of the nuclei were positive for MIB1. (E) The tumor cells were diffusely immunoreactive for p53. (F) None of the tumor cells were immunoreactive for EGFR. magnification, x200. H&E, hematoxylin and eosin; EGFR, epidermal growth factor receptor.

tumor cells were diffusely immunoreactive for p53 (Fig. 3E), but none were immunoreactive for EGFR (Fig. 3F). Wild-type IDH1 was identified by direct sequencing (Fig. 2D). The patient received radiotherapy with concomitant and adjuvant temozolomide chemotherapy and there was no evidence of recurrence during the subsequent 16-month follow-up.

Discussion

Cerebellar GBMs are a rare condition. Reports on cerebellar GBMs have described between one to seven cases and there are only a few series analyzing more than 10 cerebellar GBMs (7,8). Its rarity hampers the identification of the clinical features and biology of this tumor, as compared with the well-understood supratentorial GBMs. The present study examined a total of 10 cases of cerebellar GBMs, of which six cases were identified at Kumamoto University Hospital and four cases at affiliated hospitals. Cerebellar GBMs were compared with supratentorial GBMs, focusing on clinical features.

Clinical factors other than the KPS score did not differ between the patients with these two types of GBMs. The KPS score with cerebellar GBMs may have been lower due to hydrocephalus. Hydrocephalus was ameliorated by surgery, which may have affected the survival time. In the present study, no significant difference was noted in the survival time between patients with cerebellar those with supratentorial GBM. Weber *et al* (7) reviewed 45 patients with cerebellar GBMs treated between 1979 and 2004. It was suggested that the prognosis of cerebellar GBM patients appeared to be identical to that of cases with supratentorial tumors. Additionally, the authors also concluded that brain stem invasion was an adverse prognostic factor. In the present study one of the cases presented with brain stem invasion and this patient had the shortest survival time.

At Kumamoto University Hospital, six cerebellar GBMs (2.6%) were identified among 232 GBMs. The reason for the low frequency of cerebellar GBMs has not yet been elucidated. Of note, among the 10 cerebellar GBM cases, there were two neurofibromatosis type 1 (NF-1) patients and two patients who had received radiation therapy several years earlier. It was speculated that cerebellar GBMs may develop only in the setting of major prior genetic mutation.

NF-1 is one of the most common inherited autosomal dominant genetic disorders in humans, with frequencies ranging from 1 in 2,600 to 1 in 3,000 (9,10). This disease carries an increased risk of developing benign and malignant tumors of the central and peripheral nervous systems. The majority of intracranial neoplasms in children with NF-1 are thought to be pathologically consistent with pilocytic astrocytomas (PA). A number of PAs in the setting of NF-1 may arrest spontaneously and do not require intervention. Several cases with spontaneous malignant transformation of PA have been reported (11-14). However, the specimens used in the present study did not feature any PA component. The NF-1 gene located on chromosome 17q11.2, which produces neurofibromin, has a role in cell signaling (15,16). Mouse strains that lack p53 and harbor a conditional allele of the NF-1 tumor suppressor gene, resulting in negative regulation of Ras, develop malignant astrocytomas that demonstrate histological features of GBM (17). Radiation-induced GBMs are a rare complication of radiotherapy. Since the first radiation-induced GBM case was described in 1978 by Klériga *et al* (18), a number of such gliomas have been reported (19-25). The types of radiation-induced malignant glioma were GBMs in 69 (75%) and anaplastic astrocytoma in 23 (25%) out of 92 patients reported by Paulino *et al* (26). It has been suggested that radiation-induced neoplasms result from insufficient repair of ionizing radiation-induced DNA strand breaks in tumor suppressor genes or proto-oncogenes. Paulino *et al* (26) suggested that radiation-induced GBMs may be a type of secondary GBM, based on molecular genetic analyses showing p53 mutations but no EGFR amplification in these tumors. In both GBMs following NF-1 and radiation-induced GBM, p53 may have a significant role in tumorigenesis.

Returning to the original topic of cerebellar GBM, Utsuki *et al* (27) reported that all four cerebellar GBMs they

encountered were p53-positive and EGFR-negative by immunostaining. Saito *et al* (28) identified that all of the seven cerebellar GBMs they examined were EGFR-negative, and six out of the seven were p53-positive. Akimoto *et al* (29) reported four cerebellar GBMs, three of which were p53-positive. GBMs may develop *de novo* (primary GBMs) or via progression from low-grade or anaplastic astrocytoma (secondary GBMs). Primary GBMs develop in older patients and typically demonstrate genetic alterations (EGFR amplification, p16/INK4a deletion and/or phosphatase and tensin homolog mutations) at frequencies of 24-34%. Secondary GBMs develop in younger patients and frequently overexpress platelet-derived growth factor and cyclin-dependent kinase 4 as well as p53 mutations (65%) and loss of retinoblastoma protein are observed, all of which have major roles in such transformations (4). Immunostaining results indicated cerebellar GBMs to be of the secondary type. In the present study, immunostaining yielded the same result. Recently, a large-scale verification study revealed IDH1 mutations in 50-80% of patients with grade 2 astrocytomas, oligodendrogliomas or secondary GBMs, whereas IDH1 mutations were rare in patients with primary GBMs (6,30-37). If cerebellar GBMs are of the secondary type, a high frequency of IDH1 mutation would be expected. The IDH1 status of five cerebellar GBMs was investigated by direct sequencing. The wild-type of the IDH1 gene was detected in all five cases. In addition, Utsuki *et al* (27) detected wild-type IDH1 in all four cerebellar GBMs they examined by immunostaining. These results contradict the hypothesis that cerebellar GBMs are of the secondary type. Taking these observations together with the rarity of cerebellar GBM, it is reasonable to suggest that there are additional pathways underlying the development of cerebellar GBM, different from those leading to either primary or secondary GBM. Therefore, it is apparent that further analyses of a larger number of patients are necessary.

In conclusion, the present study confirmed cerebellar and supratentorial GBMs to essentially be identical with respect to clinical features. Furthermore, it was suggested that cerebellar GBMs may develop via pathways different from those of either primary or secondary GBM.

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