Brain Tumor Pathol (2016) 33:40–49
DOI 10.1007/s10014-015-0234-4

CASE REPORT

BRAF V600E-mutated diffuse glioma in an adult patient: a case report and review

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Received: 17 July 2015 / Accepted: 24 September 2015 / Published online: 7 October 2015

Abstract Recent advances in genomic technology and genome-wide analysis have identified key molecular alterations that are relevant to the diagnosis and prognosis of brain tumors. Molecular information such as mutations in isocitrate dehydrogenase (*IDH*) genes or 1p/19q co-deletion status will be more actively incorporated into the histological classification of diffuse gliomas. *BRAF* V600E mutations are found frequently in circumscribed low-grade gliomas such as pleomorphic xanthoastrocytoma (PXA) and extra-cerebellar pilocytic astrocytoma, or epithelioid glioblastomas (E–GBM), a rare variant of GBM. This mutation is relatively rare in other types of diffuse gliomas, especially in adult onset cases. Here, we present an adult onset case of *IDH* wild-type/*BRAF* V600E-mutated diffuse glioma, evolving from grade III to grade IV. The tumor displayed atypical exophytic growth and had unusual histological features not fully compatible with, but indicative of PXA and E-GBM. We discuss differential diagnosis of the tumor, and review previously described diffuse gliomas with the *BRAF* V600E mutation.

Keywords Anaplastic astrocytoma · Glioblastoma · BRAF mutation

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Introduction

Diffuse gliomas are primary central nervous system tumors, classified as grade II, III and IV by the World Health Organization (WHO) [1]. Grade II and III gliomas often recur and tend to progress to higher grade gliomas, eventually to secondary glioblastoma (GBM). Recent advances in genomic technology and genome-wide analysis have identified key molecular alterations that are relevant to the diagnosis and prognosis of glial tumors [2–5]. Adult onset diffuse gliomas have highly frequent mutations in the isocitrate dehydrogenase (*IDH*) 1 or 2 genes [4, 6–8]. *IDH* mutations are typically accompanied by 1p/19q co-deletions or by *TP53* mutations in mutually exclusive manner. The status of the 1p/19q co-deletion and *TP53* mutation are significantly related to the clinical outcome of *IDH*-mutated diffuse gliomas [9–11]. Wild-type *IDH* diffuse gliomas, accounting for around one-fifth of the diffuse gliomas, have a poorer outcome compared to mutated *IDH*-type gliomas [12].

BRAF point or fusion mutations are also driver mutations in glial and glioneuronal tumors, especially in pediatric onset cases [13–18]. The majority of *BRAF* mutations are missense mutations at amino acid position 600 that change a valine into a glutamate (*BRAF* V600E) [17, 19, 20]. The mutated *BRAF* protein is constitutively activated and enhances proliferation potential through the MAPK/ERK signaling pathway [15–17, 19, 20]. *BRAF* V600E is

frequently found in pleomorphic xanthoastrocytoma (PXA), ganglioglioma (GG) and extra-cerebellar pilocytic astrocytoma [17, 21, 22]. Previous reports indicated that *BRAF* V600E is also associated with epithelioid GBM (E-GBM), a rare variant of GBM [23–27]. In contrast, *BRAF* V600E mutations are reported to be rare in diffuse gliomas [12, 17].

Here, we present a rare case of a wild-type *IDH*/*BRAF* V600E-mutated diffuse glioma, progressing to GBM. We discuss differential diagnosis of the tumor, and review previously reported diffuse glioma cases with the *BRAF* mutation.

Clinical summary

A 37-year-old woman was admitted to our hospital with left hemiparesis and homonymous hemianopia. Her past medical history, including epilepsy, was negative. A slightly hyper-dense mass without cysts and calcifications was found by computed tomography (CT) scans in the right temporal lobe (Fig. 1a). Magnetic resonance imaging (MRI) revealed a lobulated 6.0 × 6.0 cm lesion in the right temporal lobe with nearly homogenous enhancement that extended exophytically into the supra- and retrosellar space (Fig. 1b–d). When removed, the tumor had an intra-axial origin, growing exophytically around the brain stem, and tended to engulf cranial nerves and major vessels. After subtotal removal of the tumor, conventional radiotherapy and chemotherapy with temozolomide were performed. Seventeen months after the first operation, the patient was re-operated because of recurrence. The tumor had the same characteristics as when operated the first time and was subtotally resected. In addition, the patient underwent cyber knife radiosurgery and immunotherapy. Her state of consciousness and physical status gradually deteriorated, and she died from pneumonia 2 years after reoperation.

Pathological findings

The tumor had an infiltrative margin, and was mainly composed of plump, round eosinophilic cells with short processes (Fig. 1e, f). Cells with scant cytoplasm and elongated thin processes were also present. Nuclei of the plump cells were occasionally hyperchromatic with prominent nucleoli, and were located eccentrically. A small number of multinucleated cells were also present. Some of these cells contained small- to medium-sized vacuoles (Fig. 1g). A few eosinophilic granular bodies were found (Fig. 1h). There was perivascular lymphocytic cuffing (Fig. 1e), but without increased reticulin fiber deposition, pseudopalisading necrosis and microvascular proliferation. Mitotic rates were 5 per 10 high power fields. The immunohistochemical study was performed with a Ventana XT system (BenchMark® XT; Ventana Medical Systems, Inc., Tuscon, AZ, USA). Sections for nestin, IDH1-H and IDH1-S were probed with primary antibodies diluted in Immuno Shot Mild (Cosmobio, Tokyo, Japan) and were immunostained using the Histofine Simple Stain MAX-PO kit (Nichirei, Tokyo, Japan). INI1 was probed with the EnVision™ System (DAKO Corporation, Carpinteria, CA, USA). The tumor cells were positive for GFAP (Fig. 1i); the cytoplasm of the plump cells was particularly well stained. Expression of nestin, S100 protein and vimentin was strong and diffuse. Many of the tumor cells contained CD34 immunoreactivity (Fig. 1j). The MIB-1 LI was 9.2 % in the main area. The results of the immunohistochemical analysis are summarized in Table 1.

The histological features of the tumor were similar after both resections. The number of tumor cells with enlarged hyperchromatic nuclei and scant cytoplasm increased (Fig. 1k). A higher degree of nuclear pleomorphism was noted, and the multinucleated cells increased in number. There was microvascular proliferation and small foci of necrosis at the periphery of the section. Mitotic figures increased up to 12 mitoses per 10 high power fields. Expression of GFAP was generally decreased compared to the first surgical specimens. The MIB-1 LI peaked at 19 % in the high cellular areas. Expression of CD34 was diffuse in almost all areas. It was observed in differentiated astrocytic, small immature and pleomorphic cells, but became weak in hypercellular areas of the second resection. The tumor cells in both resections were partially positive for neuronal markers such as synaptophysin (<10 %), neurofilament (<3 %) and chromogranin A (<30 %, and generally weak). The tumor was weakly but diffusely positive for p16 and EGFR. Expression of INI1 was preserved in the tumor cells.

Genetic study revealed a *BRAF* V600E mutation in the initial surgical material. No mutations in exon 4 of *IDH1* and *IDH2* were found. DNAs were extracted from paraffin-embedded sections. Specimens were deparaffinized, followed proteinase K digestion (Sigma Aldrich, 10 mg/sections), and extracted DNAs were subjected to amplification (Perkin Elmer 9700). The primers for *BRAF* were F 5′-TGCTTGCTCTGATAGGAAAATG-3′ and R 5′-CCAC AAAATGGATCCAGACA-3′ (exon 15, NM_004333), for *IDH1* were F 5′-AATGAGCTCTATATGCCATCACTG-3′ and R 5′-AATCACATTATTGCCAACCATGACTTAC TTG-3′ (exon 4, NM_005896 in GenBank), and for *IDH2* were F 5′-ATCCCACGCCTAGTCCCTGGCTGGACC AAG-3′ and R 5′-CAGAGACAAGAGGATGGCTAGGC GAGGAGC-3′ (exon 4, NM_002168). Products were directly sequenced on a 3730xl DNA Analyzer (Applied Biosystems, Foster City, CA) with the Big Dye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems).

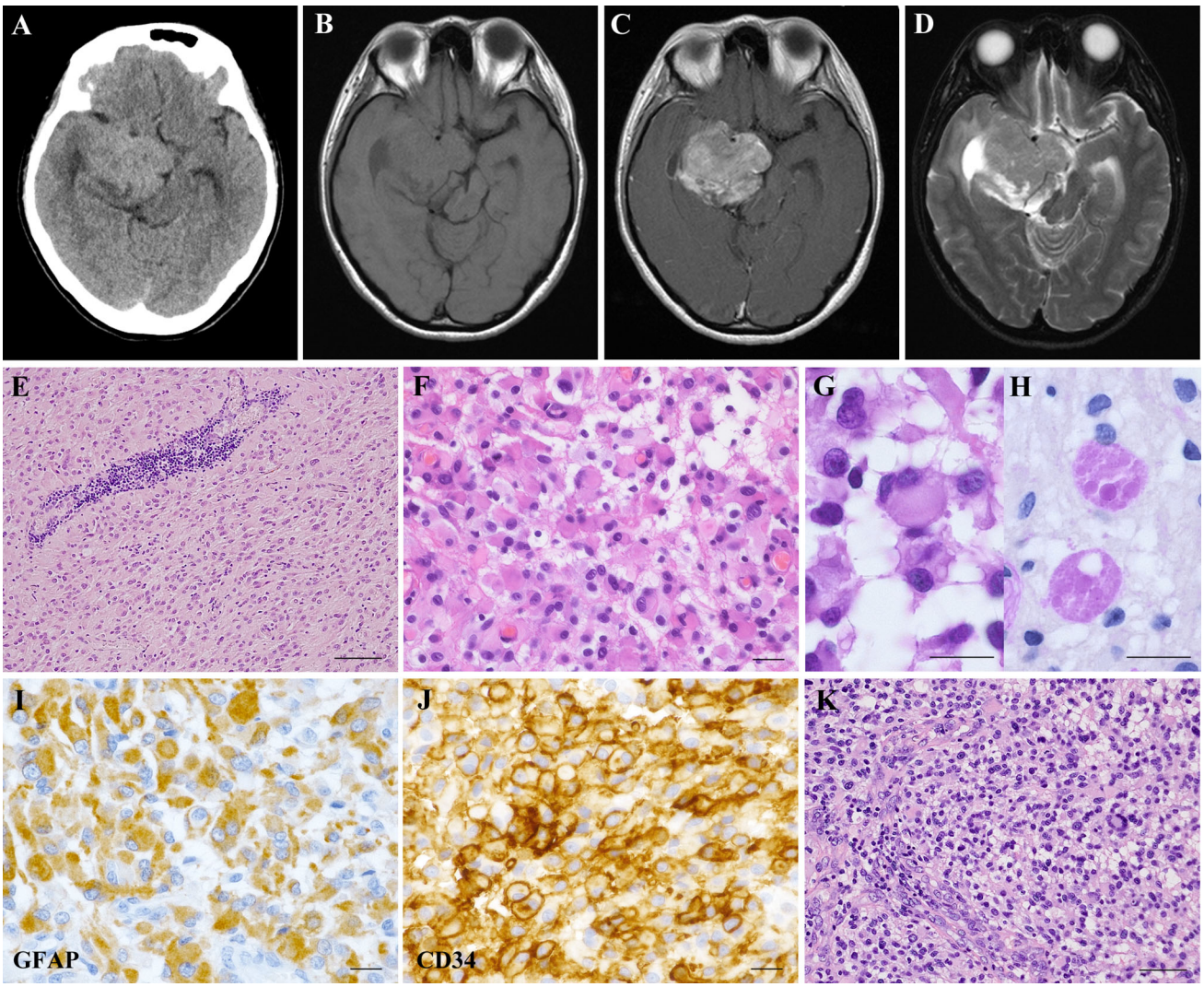

Fig. 1 Computed tomography (CT) scans and magnetic resonance images (MRI) taken before the first operation (**a**–**d**). The tumor was slightly hyper-dense on CT scans (**a**), slightly low-intensity on T1-weighted images (**b**), T1-weighted gadolinium-enhanced MRI revealed a nearly homogenous enhanced mass, without regions of poor contrast enhancement (**c**), slightly high-intensity on T2-weighted images (**d**). Pathological features of the tumor after the first resection (**e**–**j**). The plump, eosinophilic cells with short processes proliferated diffusely, and perivascular lymphocytic cuffing was observed (**e**, **f**). Tumor cells with small to medium sized vacuoles and PAS-positive eosinophilic granular bodies were present (**g**, **h**). The tumor cells were positive for GFAP (**i**) and CD34 (**j**). After the second resection, the tumor showed increased cellularity and pleomorphism with microvascular proliferation (**k**). **e**–**g**, **k** Hematoxylin and eosin. **h** Periodic aid-Schiff stain. **i** Immunohistochemistry (IHC) for GFAP. **j** IHC for CD34. **e**, **k** *Bar* 50 μm. **f**–**j** *Bar* 20 μm

Discussion

The tumor displayed atypical radiographic features; its growth was apparently exophytic and it had well-demarcated borders. Pathologically, the tumor consisted of GFAP-positive cells with abundant cytoplasm and short stellate processes or scant cytoplasm with elongated processes. Mitotic rates were high, and the tumor was diagnosed as a Grade III anaplastic astrocytoma (WHO classification 2007) [1]. However, the tumor had some specific features. There was a small but not negligible number of multinucleated cells with vacuolated cytoplasm. The presence of a few eosinophilic granular bodies, perivascular cuffing and CD34 immunoreactivity suggested that the tumor shared some pathological characteristics with circumscribed gliomas such as PXA or GG. The tumor cells expressed neuronal markers, synaptophysin, NF and chromogranin A with variable frequency. These cells were morphologically indistinguishable from other astrocytic cells, and not taken to be neuronal components.

It is still debatable whether the tumor should be categorized as a circumscribed/localized astrocytoma. Histological examination of circumscribed gliomas often shows

Table 1 Immunohistochemical profile in the tumor

	GFAP	Vim	S-100	Nestin	Olig2	Syn	NF	Chromo	CD34	CK	EMA	P16	EGFR	INI1	p53 (%)	Ki-67 (%)	IDH1-H	IDH1-S
First	+	++	++	++	+	±	±	±	+	–	–	+	+	+	18	9.2	–	–
Second	±	++	++	++	+	±	±	±	+	–	–	+	+	+	20	19	–	–

GFAP glial fibrillary acid protein (DAKO, rabbit, polyclonal), *Vim* vimentin (novocastra, mouse, clone V9), *S-100* (DAKO, rabbit, polyclonal), *Nestin* (IBL, rabbit, polyclonal), *Olig2* (IBL, rabbit, polyclonal), *Syn* synaptophysin (novocastra, rabbit, clone 27G12), *NF* neurofilament (DAKO, mouse, clone 2F11), *Chromo* chromogranin A (DAKO, mouse, clone DAK-A3), *CD34* (BD Biosciences, mouse, clone My10), *CK* cytokeratin (BD Biosciences, mouse, clone CAM 5.2), *EMA* epithelial membrane antigen (DAKO, mouse, clone E29), *p16* (abcam, rabbit, clone EPR1473), *EGFR* (novocastra, mouse, clone EGFR.113), *INI1* (Abnova, mouse, clone 3E10), *p53* (novocastra, mouse, clone DO-7), *Ki-67* (DAKO, mouse, clone MIB-1), *IDH1-H* (DANOVA, mouse, clone H09), *IDH1-S* (IBL, mouse, clone SMab-1)

an infiltrative margin as in the present case. The most important differential diagnosis for this case is PXA with anaplastic features. The tumor lacked the classical features of PXA: proliferation of spindle cells with fascicular patterns and a reticular formation. Basically, the tumor was composed of fibrillary or gemistocytic astrocytic cells. Pleomorphism was not prominent; only a small number of vacuolated cells and eosinophilic granular bodies were detected by careful re-evaluation. Anaplastic astrocytomas rarely, but can show exophytic growth [28]. Taking these pathological features into consideration, we tentatively diagnosed the tumor as an anaplastic astrocytoma. Chi et al. [29] reported 7 adult cases of *BRAF*-mutated diffuse gliomas with atypical radiographic and histological features. They described the gliomas as infiltrating, but with relatively well-demarcated borders, similar to the tumor we described here. The atypical histological features described by the authors included the presence of ependymal-like cells, proliferation of spindle tumor cells into subarachnoid and Virchow-Robin spaces, and piloid growth of tumor cells with Rosenthal fibers. Although the atypical pathological features mentioned by the authors were not necessarily compatible with those of our case, it should be noted that *BRAF*-mutated diffuse gliomas have somewhat "unusual" histological features.

The *BRAF* V600E mutation is rare in diffuse gliomas, but certain number of cases has been reported [12, 16–19, 22–27, 29–51]. Through a literature search, total 113 diffuse gliomas were listed (Table 2): 38 cases of grade II, 14 cases of grade III including 2 gliomatosis cerebri, 54 cases of grade IV, 2 cases of grade II–III, and 5 case of grade III–IV. When available, age and gender of the patients, location of the tumor, *IDH1* mutation and 1p/19q status were recorded in the table. As previously reported, the *BRAF* V600E mutation was found preferentially in young patients; 56 patients were 20 years of age or under. Pediatric gliomas and glioneuronal tumors have molecular backgrounds that differ from adult tumors [18, 48]. *IDH* mutations, a major mutation in adult grade II and III diffuse gliomas, are rare in pediatric gliomas [16, 18, 50]. *BRAF* V600E mutations were found in 23 % of low-grade diffuse astrocytomas in a large cohort of low-grade pediatric gliomas [18]. Ramkissoon et al. [43] also reported a similar frequency of *BRAF* V600E mutations in diffuse pediatric astrocytomas; however, this mutation is rare in diffuse adult gliomas, in which the prevalence is estimated at less than 1 % [12].

Affected females seemed to predominate in the listed tumors (39 female, 29 male cases); however, the gender of the other 45 cases was unknown. Most commonly, *BRAF*-mutated diffuse gliomas arise from the cerebral cortex; the temporal and temporo-parietal lobes seem to be most frequently affected (19 cases).

Table 2 The previously reported BRAF mutation in gliomas

Type	BRAF mutations	Age (year)	Gender	Location	*IDH1*	1p/19q	Other information	References
DA	MacConaill et al. [34]	Pediatric					Astrocytoma WHO Grade II	[34]
	Sievert et al. [35]	13	F	Bithalamic				[35]
	Schiffman et al. [16]	19		Brain stem			DLGA, *CDKN2A* (D)	[16]
		20		Occipital			DLGA, *CDKN2A* (D)	
	Kim et al. [39]	1 Case		Temporal	+		A598 V	[39]
	Chi et al. [29]	41	F	Rt. parietal				[29]
		30	F	Rt. temporal				
		22	F	Lt. temporal				
		28	M	Rt. temporal				
	Ramkissoon et al. [43]	1.4	F	Forebrain				[43]
		5.6	M	Forebrain				
		8.3	F	Forebrain				
		13	M	Forebrain				
	Zhang et al. [18]	3	M	Cerebral cortex				[18]
		3	M	Cerebral cortex				
		3	F	Cerebral cortex				
		9	M	Cerebral cortex				
		10	F	Diencephalon				
	Roth et al. [47]	11	M				An indeterminate subtype LGG	[47]
	Gierke et al. [48]	3 Pediatrics (0–18)						[48]
OA	Chi et al. [29]	32	F	Lt. temporal		–		[29]
OG	Jeuken et al. [32]	1 Case					V600 M	[32]
	Schindler et al. [17]	39	M	Lt. temporal	–	–		[17]
	Myung et al. [41]	53			+	+		[41]
	Badiali et al. [37]	1 Case			–	–		[37]
	Kim et al. [39]	1 Case		Rt. occipital	–	L		[39]
DA, OG, NOS	Horbinski et al. [38]	Pediatric		Cerebellum				[38]
LGG	Korshunov et al. [49]	1	F	Midline	–			[49]
		1	M	Midline	–			
		11	M	Hemispheric	–			
		7	F	Hemispheric	–			
LGG-NOS	Ramkissoon et al. [43]	10.2	F	Cerebellum				[43]
		10.6	M	Forebrain				
		10.2	F	Brain stem				

Table 2 continued

Type	BRAF mutations	Age (year)	Gender	Location	*IDH1*	1p/19q	Other information	References
		10.2	M	Forebrain				
		15.8	F	Forebrain				
AA	Schiffman et al. [16]	13		Temporal				[16]
		5		Frontal			*CDKN2A* (D)	
		13		Cerebellum				
	Schindler et al. [17]	Pediatric						[17]
		Pediatric						
	Lin et al. [40]	1 Case						[40]
	Myung et al. [41]	35	F		+	−		[41]
		39	F		+	−		
		50	M		−	−		
		53	F		−	−		
AO	Myung et al. [41]	45	M		+	+		[41]
	Badiali et al. [37]	1 Case			+	+		[37]
G2-3 glioma	Suzuki et al. [12]	Adults 2 cases			−	−		[12]
GC	Schindler et al. [17]	77	F	Lt. temporal with spread in frontal and occipital				[17]
	Fernandez-Vega et al. [45]	67	F	Brain stem and cerebellar hemispheres	−		Involving cerebral hemisphere and spinal cord	[45]
C-GBM	Knobbe et al. [30]	Adults 2 cases					V599E	[30]
	Basto et al. [31]	46						[31]
		41						
	Hagemann et al. [33]	1 Case						[33]
	Schiffman et al. [16]	17		Parietal			*CDKN2A* (D)	[16]
		17		Parietal			*CDKN2A* (D)	
	Nicolaides et al. [36]	6 Cases						[36]
	Schindler et al. [17]	2 Pediatrics						[17]
		46	F		−		Progressed from DA	
	Myung et al. [41]	53	M					[41]
	Bettegowda et al. [42]	17		Rt. temporoparietal				[42]
		18		Rt. temporal				
		Petiatric					1 of additional 6 pediatric GBM	
	Chi et al. [29]	23	F	Rt. parietal	−			[29]
		66	M	Rt. parietal	−			
	Bleeker et al. [44]	1 Case						[44]

Table 2 continued

Type	BRAF mutations	Age (year)	Gender	Location	*IDH1*	1p/19q	Other information	References
	Robinson et al. [46]	9		Rt. frontoparietal				[46]
	Roth et al. [47]	2	M		–		*CDKN2A* (D)	[47]
	Mistry et al. [50]	Pediatric, 9<	M	Hemispheric	–		Progressed from LGG	[50]
		Pediatric, 9<	M	Hemispheric	–		*CDKN2A* (D), Progressed from PA	
		Pediatric, 9<	M	Hemispheric	–		*CDKN2A* (D), Progressed from PXA	
		Pediatric, 9<	M	Hemispheric	–		*CDKN2A* (D), Progressed from LGA	
		Pediatric, 9<	F	Midline	–		Progressed from LGA [*CDKN2A* (D)]	
	Takahashi et al. [51]	49	M	Rt. parietooccipital	–		Recurrence after 22 months	[51]
E-GBM	Kleinschmidt-DeMasters et al. [23]	27	F	Lt. occpital	–			[23]
		43	M	Lt. temporoparietal	–			
		10	F	Rt. parietooccipital	–			
		29	M	Lt. temporal	–			
		21	F	Rt. temporal	–			
		29	F	Lt. temporoparietal	–			
		50	M	Lt. temporal	–			
	Broniscer et al. [24]	10	F	Thalamus	–			[24]
		11	M	Temporal	–			
		10	F	Bithalamic	–			
	Nobusawa et al. [25]	22	M	Rt. occipital	–			[25]
	Tanaka et al. [26]	25–26	F	Lt. temporal			Progressed from PXA	[26]
	Kleinschmidt-DeMasters et al. [27]	55	M	Lt. temporal	–			[27]
		39	F	Lt. frontal	–			
		32	F	Rt. parietal	–			
		69	M	Lt. parietal	–			
R-GBM	Myung et al. [41]	20	F		–	–		[41]

Table 2 continued

Type	BRAF mutations	Age (year)	Gender	Location	*IDH1*	1p/19q	Other information	References
GC-GBM	Schindler et al. [17]	22	F				Progressed from DA	[17]
	Dias-Santagata et al. [22]	30	F	Lt. temporal			Progressed from PXA	[22]
		1 Case						
	Myung et al. [41]	36	F		–	–		[41]
HGG	MacConaill et al. [34]	Pediatric						[34]
	Korshunov et al. [49]	8	F	Midline	–			[49]
		13	F	Midline	–			
		7	F	Midline	–			
		8	F	Midline	–			
Gliosarcoma	Knobbe et al. [30]	1 Case					V599E	[30]
	Schindler et al. [17]	32			–	–		[17]

DA diffuse astrocytoma, *OA* oligoastrocytoma, *OG* oligodendroglioma, *NOS* not otherwise specified, *LGG* low-grade glioma, *AA* anaplastic astrocytoma, *AO* anaplastic oligodendroglioma, *G2-3 glioma* grade II and III gliomas, *GC* gliomatosis cerebri, *C-GBM* classical glioblastoma, *E-GBM* epithelioid GBM, *R-GBM* rhadboid GBM, *GC-GBM* giant cell GBM, *HGG* high grade glioma, *f* female, *m* male, *rt.* right, *lt.* left, *IDH1+* mutation, *IDH1−* no mutation, *1p/19q+* co-deletion, *1p/19q−* no co-deletion, *L* 1p/19q loss, *DLGA* diffuse infiltrating low-grade astrocytoma, *CDKN2A (D) CDKN2A* deletion, *LGA* low-grade astrocytoma, *Ref.* reference number, *blank* not in detail

Among the grade II and III gliomas, 34 cases were astrocytic, 7 cases were oligodendrocytic, one case was oligoastrocytic; the other 12 cases were unspecified. An *IDH1* mutation was detected in 6 of the 50 cases investigated: 1 case of diffuse astrocytoma (DA), 2 cases of anaplastic astrocytoma (AA), 1 case of oligodendroglioma (OG) and 2 cases of oligodendroglioma (AO). One case of *IDH*-mutated OG and 2 cases of AO had concomitant 1p/19q co-deletions. Thus, *IDH* mutations, 1p/19q co-deletions and *BRAF* V600E mutations are not necessarily mutually exclusive [37, 41]. The 3 gliomas harboring these three molecular events contained oligodendrocytic components. Neither *IDH* mutations nor 1p/19q co-deletions were found in the grade IV glioblastomas. Of note, 10 cases of *BRAF*-mutated diffuse astrocytomas had deletions of *CDKN2A*, known to be found frequently in PXA [52], and all cases were 20 years of age or under [16, 47, 50]. Recent reports indicated that secondary pediatric high grade gliomas with *BRAF* mutation and *CDKN2A* deletion arose from low-grade counterparts after long latency, and showed favorable clinical outcomes compared to GBMs without these molecular alterations [49, 50].

A close association between *BRAF*V600E mutations and E-GBM has been reported. The other types of grade IV glioblastomas than E-GBM are also associated with this type of mutation (Table 2). Some of the *BRAF*-mutated GBMs, with both classical and variant histology, progressed from preexisting low-grade gliomas [17, 22, 26, 50], as in our case. Kleinschmidt-DeMasters et al. [23] examined 13 E-GBM, 2 Rhabdoid GBM (R-GBM) and 9 Giant cell GBM (GC-GBM) cases, and identified *BRAF* V600E mutations in 7/13 (54 %) E-GBMs, but not in R-GBMs or GC-GBMs. E-GBM, a rare morphological variant of glioblastoma, was not yet defined in the 4th edition of WHO classification in 2007. E-GBMs are composed of patternless sheets of "melanoma-like" epithelioid cells with round eosinophilic cytoplasm and eccentrically located nuclei. These cells are discohesive and devoid of stellate cellular processes [53–55]. In our case, eosinophilic round cells, somewhat resembling epithelioid cells, proliferated. However, the cells generally had short thin stellate processes (Fig. 1f, g). When the tumor progressed to Grade IV, tumor cells with faint cytoplasm predominated (Fig. 1k). Large, round mono- or multinucleated eosinophilic cells were also present. These cells were not "melanoma-like", but resembled the atypical glial cells in classical GBMs. We considered that the histological features of our case were not necessarily compatible with those of E-GBM. As discussed above, the tumor shared some pathological characteristics with PXA. A case of E-GBM arising from PXA was previously reported [26]. Very recently, Alexandrescu et al. reported a series of PXA cases with anaplastic foci resembling E-GBM [56].

Importantly, these cases were strongly associated with *BRAF*V600E mutations. Our case had histological features not fully compatible with, but indicative of, PXA and E-GBM. Clear histological definition of PXA-E-GBM lineage tumors will be needed for accurate classification of tumors harboring pathological features that are difficult to interpret, as in our case.

R-GBM is also a rare variant that shares some overlapping morphological features with E-GBM [23, 55]. GC-GBM is composed of bizarre, multinucleated giant cells, with occasional reticulin deposits; it was defined as a subtype of GBM in the WHO classification [1]. Histological definitions of these rare subtypes have not been clearly established yet, and these variants are often confused. Inactivation of INI1 is considered to be associated with rhabdoid tumor cells, and focal loss of INI1 protein has been proposed to be an important indicator for the diagnosis of R-GBM [23, 55, 57]. INI1 expression was not examined in all of the cases. Careful re-evaluation will be needed to clarify how the molecular alteration, *BRAF* mutation, INI1 inactivation and other molecular events that have not yet been evaluated, relate to the histological variants of GBMs.

Our patient survived 2 years after the diagnosis of GBM and multimodal treatments. Some reports indicated that *BRAF* V600E mutations might be a favorable prognostic factor in adult GBMs with classical histology [29, 58]. In contrast, E-GBMs, in which *BRAF* mutations are frequent, are known to have an aggressive clinical behavior [24, 26]. The prognostic significance of *BRAF* mutations in diffuses gliomas should be addressed through longer follow-up of large glioma cohorts. From now on, molecular information with prognostic, predictive and therapeutic value will be actively incorporated into the histological classification of brain tumors. Importantly, the *BRAF* V600E mutation can be a therapeutic target in glial tumors [14, 36, 46]. Therefore, to find this molecular alteration efficiently, further elucidation of the clinico-pathological features of *BRAF*-mutated diffuse gliomas will be necessary.

Acknowledgments We thank Dr. M Ruberg for a critical reading of the manuscript, Drs. Shinji Ito and Dr. Takashi Komori for the immunohistochemistry, and the latter for kind advice concerning the diagnosis.

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