CASE REPORT

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RHABDOID GLIOBLASTOMA: AN AGGRESSIVE VARIATY OF ASTROCYTIC TUMOR

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ABSTRACT

Rhabdoid glioblastoma (RGBM) is rare, but the most malignant among astrocytic tumors. Accumulating evidence indicates its highly aggressive nature and distinct histopathological features. Here, we report a new case of RGBM and review previously reported cases of astrocytic tumors with rhabdoid components. We describe a 58-year-old man who presented with aphasia and right-sided weakness. Magnetic resonance imaging revealed a well-delineated intramedullary tumor in the left cerebral hemisphere. Partial resection of the tumor was performed. The tumor was histologically found to contain two distinct areas: a typical glioblastoma, and a rhabdoid component. Immunohistochemical analyses revealed expression of glial fibrillary acidic protein (GFAP) and focal loss of the INI1 protein in rhabdoid cells, although fluorescence *in situ* hybridization analysis showed no loss of the *INI1* gene. Despite subsequent radiochemotherapy for the glioblastoma, the patient died 4.3 months after surgery. Our literature review illustrates the aggressive clinical course and histopathological features of these tumors with GFAP and INI1 expression. INI1 protein dysfunction may be a possible cause of the rhabdoid phenotype. Gross total resection of the tumor and intensive radiochemotherapy may lead to better survival outcomes.

Key Words: rhabdoid glioblastoma, astrocytic tumor, INI1, GFAP, adult

INTRODUCTION

Rhabdoid tumors consist of cells that have vesicular nuclei and abundant eosinophilic cytoplasm; they can arise everywhere in the body, including the central nervous system (CNS).[1,2] Among these tumors, malignant rhabdoid tumors (MRTs) occur as part of a genetic disorder specifically involving the CNS and kidneys and characterized by mutation or deletion of the *INI1* gene.[3] An atypical teratoid/rhabdoid tumor (AT/RT) is the pediatric manifestation of primary MRTs in the CNS.[4] *INI1* deletions or mutations are reportedly observed in 78% of AT/RT cases and the INI1 protein is lost in all cases.[5-7] Primary CNS tumors with rhabdoid features, but without INI1 abnormality, have also been identified. Meningioma, glioma, and primitive neuroectodermal tumor (PNET) cells can potentially show diverse differentiation.[8-26]

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However, the genetic and histological origins of these rhabdoid cells are still unknown. Rhabdoid glioblastoma (RGBM) is a recently recognized rare astrocytic tumor with a rhabdoid component. RGBM preferentially occurs in young patients and is highly aggressive, with early recurrence and leptomeningeal spread.[14-25] Here, we report a new case of supratentorial RGBM in an adult male. In addition, we present a literature review and discuss the histopathological and clinical features of astrocytic tumors with rhabdoid components.

CASE REPORT

A 58-year-old right-handed man presented with aphasia and mild right-sided weakness, and was admitted to Sapporo Shiroishi Memorial Hospital. He had no significant personal or family medical history. Cranial magnetic resonance (MR) imaging of his brain revealed a well-delineated solid tumor, 60 mm in diameter, with heterogeneous contrast enhancement and marked perifocal edema in the left basal ganglia (Fig. 1, A and B). Diffusion weighted images showed predominant high signal intensity areas, implying the hypercellular nature of the tumor (data not shown). MR spectroscopy showed a high lipid/lactate peak, suggesting necrotic lesions in the tumor (Fig. 1C). Digital subtraction angiography of the brain was performed and slight tumor staining was observed in the late venous phase (data not shown). As a metastatic brain tumor was initially suspected, chest and abdominal computed tomography scans and serological examination of tumor markers were performed; these revealed no evidence of systemic malignancy. The patient underwent tumor excision through a left pterional approach. Macroscopically, the tumor consisted of two components, a reddish soft tumor and yellowish hard tumor. The border between the tumor and normal brain tissue was unclear. About 50% of the tumor was resected. After the surgery, his symptoms of aphasia and right hemiparesis worsened, and he was referred to Sapporo Medical University Hospital for postoperative therapy with a Karnofsky performance status (KPS) of 50%. The patient was administered radiotherapy (comprising of 2-Gy daily fractions of focal irradiation administered 5 days a week for 6 weeks; total dose, 60 Gy) and concomitant chemotherapy with temozolomide (75 mg/m^2/day, planned for administration daily for 6 weeks). However, the chemotherapy was terminated after 12 days because of nausea, appetite loss, and difficulty with oral intake, despite steroid administration. The patient was transferred to another hospital for palliative care with a KPS of 40%, and succumbed to his brain tumor 130 days after the surgery.

Histological examination revealed glioblastoma multiforme with massive hemorrhage and necrosis (data not shown). The tumor contained both glioblastoma and rhabdoid tumor cells. The glioblastoma components showed hyperchromatic nuclei, mild pleomorphism, and microvascular proliferation (Fig. 2A), while rhabdoid components were characterized by large eccentric nuclei with prominent nucleoli and abundant eosinophilic cytoplasm (Fig. 2B). These rhabdoid cells showed focal but not intense positivity for glial fibrillary acidic protein (GFAP) (Fig. 2C). There was strong expression of vimentin in both the rhabdoid and glioblastoma cells, and focal expression of epithelial membrane antigen (EMA) in the rhabdoid cells (data not shown). Although INI1 protein expression was observed in most of the tumor area (detected by the anti-INI1 antibody [BAF47, BD Transduction Laboratories, San Diego, USA; 1:100]), there were focal areas of INI1-negative rhabdoid cells (Fig. 3A, B). Fluorescence *in situ* hybridization (FISH) analysis, using probes for chromosome 22 as described previously,[27] revealed no deletion of the *INI1* gene region (Fig. 3C). Further immunohistochemical analysis was conducted and produced results consistent with prior reports of RGBM (Table 1).

The differential diagnosis included glioblastoma with gemistocytes and epithelioid glioblastoma.

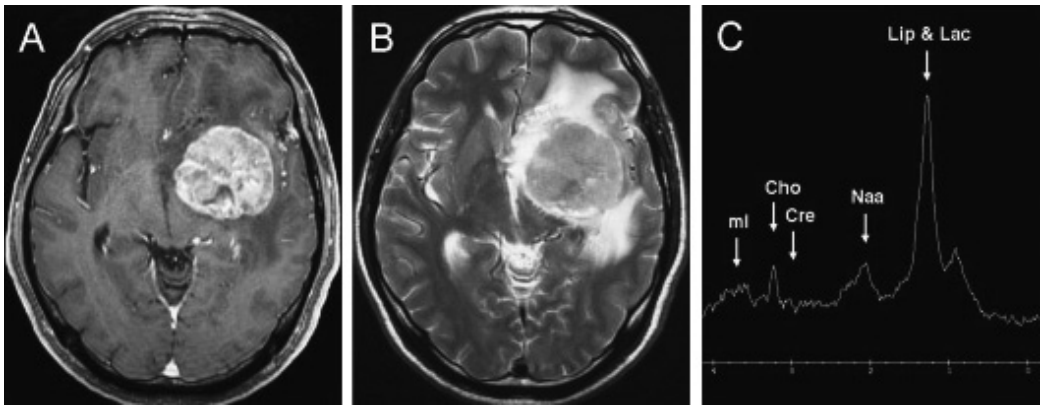

Fig. 1 Preoperative cranial magnetic resonance imaging and spectroscopy. (A) Axial T1-weighted image with gadolinium contrast showing a well-circumscribed solid tumor with strong heterogeneous enhancement in the left basal ganglia. (B) T2-weighted image showing a slightly hyperintense mass with perifocal edema. (C) Magnetic resonance spectroscopy of the tumor revealing a high lipids and lactate (Lip & Lac) peak, suggesting necrosis and an anaerobic state within the tumor. Naa, N-acetylaspartate; Cre, creatine; Cho, choline; ml, myo-inositol.

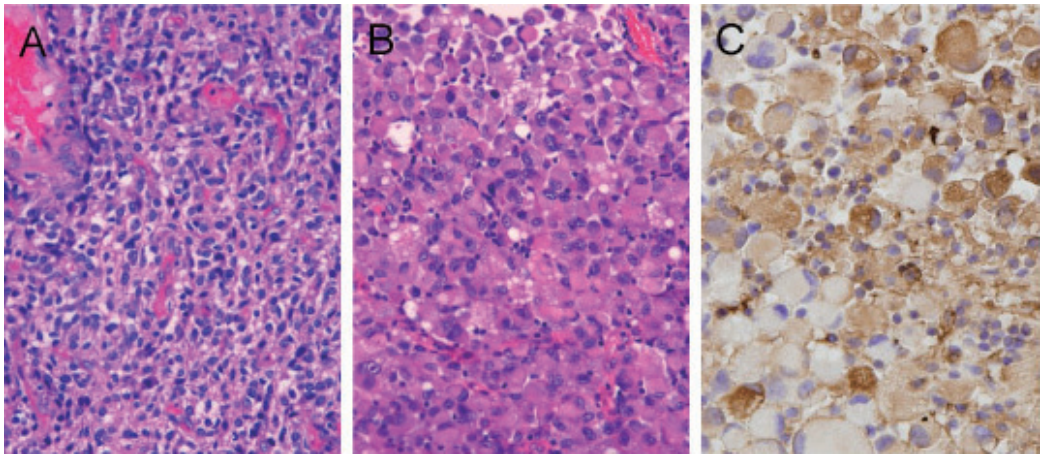

Fig. 2 Histopathological features of rhabdoid glioblastoma. (A) Glioblastoma cells with hyperchromatic nuclei and mitoses (original magnification, ×200). (B) Rhabdoid cells showing eccentric nuclei with prominent nucleoli, displaced to the periphery by the abundant eosinophilic cytoplasm, resembling gemistocytes (original magnification, ×400). (C) Immunohistochemistry for GFAP in the rhabdoid component showing focal expression, indicating astrocytic lineage differentiation (original magnification, ×400).

Gemistocytic cells resemble rhabdoid cells in morphology, but may have angulated cell bodies with fibrillated processes, and show packed glial filaments in their perikarya. In our case, however, the plump cells had no cell process, and showed only weak and focal GFAP expression. It is important to exclude epithelioid glioblastoma as well; however, it is difficult to do so because of its similar morphological features.[28-30] The tumor cells in this case were loosely cohesive or scattered and INI1 protein expression was focally lost. These findings have been reported as

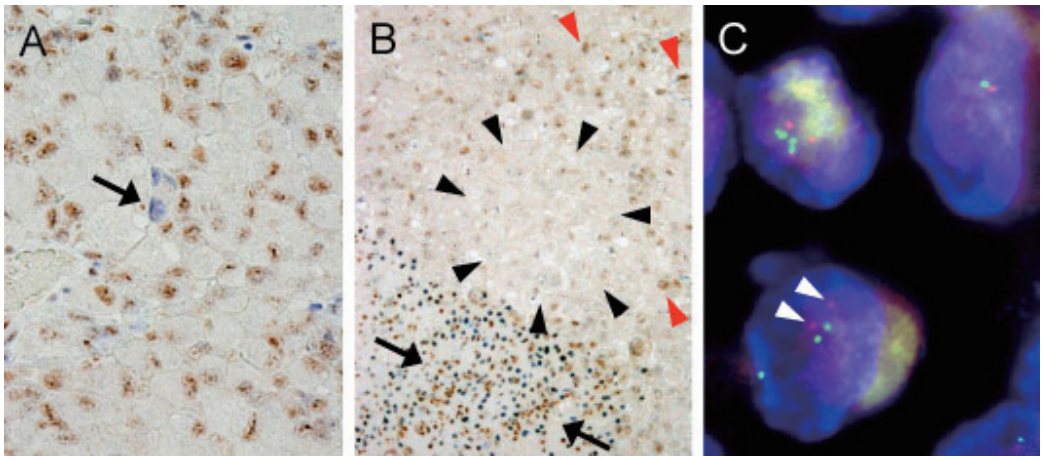

Fig. 3 Histopathological and cytogenetic features of INI1 expression in the rhabdoid component. (A) INI1 immunonegative cells are occasionally seen among rhabdoid tumor cells (black arrow) (original magnification, ×200). (B) Focal area showing the loss of INI1 protein (black arrowheads) surrounded by INI1-expressing cells (red arrowheads) in the rhabdoid component. Note the infiltrating lymphocytes as a positive staining control on the right side of the panel (black arrows) (original magnification, ×200). (C) FISH analysis demonstrating retained *INI1* gene loci in rhabdoid cells (white arrowheads): both markers are located on chromosome 22 (*centromere* in green, *INI1* in red) (original magnification, ×1000).

Table 1 Immunohistochemical expression profile in rhabdoid and glioblastoma cells

	Ki-67	p53	GFAP	NF	S-100	Olig2	VIM	EMA	AE1/3	SMA	EGFR	VEGF	INI1
Rhabdoid cells	40%	3%	+	−	−	−	++	+	−	−	++	++	+
Glioblastoma cells	20%	−	++	++	++	−	++	−	−	−	+	++	+

GFAP, glial fibrillary acid protein; NF, neurofilament; VIM, vimentin; EMA, epithelial membrane antigen; AE1/3, AE1/AE3 (pan cytokeratin); SMA, smooth muscle actin; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; −, negative; +, focally positive; ++, diffusely positive

key features in differentiating epithelioid glioblastoma from RGBM.[16,30] Thus, a diagnosis of RGBM was made.

DISCUSSION

Astrocytic tumors with rhabdoid features are relatively rare among all the CNS tumors with rhabdoid components. To date, only 23 cases of astrocytic tumors with rhabdoid components, including 20 cases of RGBM, have been published in English.[11-25] The histological characteristics of these tumors are summarized in Table 2. Rhabdoid components usually contain necrosis and show high Ki-67 staining indices ranging from 8–41%. Immunohistochemically, all cases with rhabdoid cells in astrocytic tumors show strong vimentin expression. In most cases, they also show immunoreactivity for EMA and GFAP. Most importantly, INI1 protein expression is retained in all reported cases, and a focal loss of the INI1 protein or monosomy of chromosome 22 in rhabdoid cells has been observed in several cases, including ours.[12,14-16,21,22] Among CNS tumors, complete inactivation of the INI1 protein may be a feature exclusive to MRTs,[19] while a focal

Table 2 Reported cases of astrocytic tumors with rhabdoid components

Reference	Age/sex	Pathological diagnosis	Rhabdoid tumor or component						
			Survival[a]	Nec	Ki-67[b]	GFAP[b]	VIM[b]	EMA[b]	INI1[c]
(11)	18/F	DA with rhabdoid component	0.7 mo	+	29%	+	++	+	++
(12)	23/M	OA with rhabdoid component	5.0 mo	+	40%	–	++	++	22m
(13)	16/M	LGA + MRT[d]	4.0 mo	+	high	++	++	+	N/A
(14—16)	18/M	GBM + Rhabdoid GBM[d]	3.7 mo	+	26%	+	++	+	22m
(17)	16/F	Rhabdoid GBM	3.2 mo	+	N/A	++	++	++	N/A
(18)	66/M	Rhabdoid GBM	short	+	N/A	++	++	+	22q+
(19)	36/M	Rhabdoid GBM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	20/F	Rhabdoid GBM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
(16)	67/F	Rhabdoid GBM	8.3 mo	+	18%	++	++	+	22m
(20)	31/M	Rhabdoid GBM	3.2 mo	+	8%	+	++	++	++
(21)	12/M	Rhabdoid GBM	4.9 mo	+	41%	+	++	+	+
(22)	23/F	Rhabdoid GBM[e]	4.0 mo	+	30%	+	++	++	+
(23)	19/M	Rhabdoid GBM	6.5 mo	+	35%	+	++	N/A	++
	29/M	Rhabdoid GBM	2.0 mo	+	N/A	+	++	N/A	++
(24)	30/F	Rhabdoid GBM	12 mo[f]	+	20%	++	++	+	++
	52/M	Rhabdoid GBM	43 mo	+	N/A	–	++	++	N/A
	64/M	Rhabdoid GBM	62 mo	+	N/A	N/A	N/A	N/A	N/A
	29/F	Rhabdoid GBM	12 mo	+	10%	++	N/A	++	++
(25)	20/F	Rhabdoid GBM	22 mo[f]	+	30%	+	++	++	++
	42/M	Rhabdoid GBM	21 mo	+	30%	+	++	–	++
	28/F	Rhabdoid GBM	62 mo[f]	+	15%	+	++	++	++
	43/F	Rhabdoid GBM	13 mo	+	30%	+	++	++	++
	45/F	Rhabdoid GBM	24 mo[f]	+	34%	+	++	+	++
Present case	58/M	Rhabdoid GBM	4.3 mo	+	40%	+	++	+	+

Nec, necrosis; VIM, vimentin; EMA, epithelial membrane antigen; DA, diffuse astrocytoma; OA, oligoastrocytoma; LGA, low grade astrocytoma; MRT, malignant rhabdoid tumor; GBM, glioblastoma; 22m, chromosome 22 monosomy; N/A, not available; [a], survival after the resection of rhabdoid tumor; [b], positivity or staining result of immunohistochemistry; [c], expression status confirmed by immunohistochemistry or FISH analysis; [d], secondary rhabdoid tumors; [e], described as malignant brain tumor with rhabdoid features in the original report; [f], patient is alive at the time of original publication; –, negative; +, weakly or focally positive; ++, strongly and diffusely positive.

loss of the INI1 protein is more suggestive of RGBM than epithelioid glioblastoma.[16,21,25,30]

Clinically, astrocytic tumors with rhabdoid components are characterized by their preferential occurrence in young populations and poor prognosis, resembling AT/RTs or rhabdoid meningiomas.[11-25] Tumor size at diagnosis is relatively large (median, 47 mm; range, 20–70 mm) and tumors are well enhanced under contrast-administered MRI. As the margin of the tumor is radiographically clear in most cases, its differential diagnosis from metastatic brain tumors may be difficult prior to surgery. When rhabdoid cells are prominent in the tumors, intraoperative diagnosis may also be difficult because the tumor cells of some epithelial carcinomas are morphologically similar to rhabdoid cells. The prognosis of patients has been extremely poor in

previous reports, with 4.9 months of median survival time from the time of diagnosis of their rhabdoid tumors. Multimodal treatments, including surgery, radiotherapy, and chemotherapy were applied to these tumors. Nonetheless, the effects of treatment were limited and leptomeningeal dissemination and early recurrence was frequently seen. Although recent reports have shown better survival in RGBM patients with intensive chemotherapy,[24,25] the extent of tumor resection may be the most important factor in treating these tumors.

Several tumors with rhabdoid features have been reported to arise from pre-existing glial tumors such as gangliogliomas, low grade astrocytomas, and glioblastomas,[13,14,31] suggesting rhabdoid transformation in these tumors. Pregnancy seems to be another potential risk factor for developing the rhabdoid phenotype, and it has been reported that two of the six adult women who had rhabdoid tumors were pregnant at the time of diagnosis.[32,33] INI1 protein dysfunction may be the mechanism for development of the rhabdoid phenotype. Interestingly, Kohashi *et al.* have reported infrequent *INI1* gene alteration, including mutation, but frequent loss of INI1 protein expression in epithelioid sarcoma, a rare mesenchymal soft tissue tumor with an epithelioid pattern.[34] These findings suggest that rhabdoid cells could be transformed or differentiated from other neoplastic cells, and their formation of tumors could possibly be promoted by hormonal factors or INI1 dysfunction.

In conclusion, we encountered a rare case of RGBM in an adult and reviewed the literature on astrocytic tumors with rhabdoid components. Although RGBM has not yet been recognized as a variant or pattern of glioblastoma, based on the 2007 World Health Organization (WHO) classification,[35] it meets the criteria for glioblastoma and shows distinct clinical and histopathological features.[16,25] Accumulating evidence indicates the aggressive nature of these astrocytic tumors with rhabdoid components. Multimodal treatments, with maximum tumor resection and intensive radiochemotherapy, may yield better survival outcomes. Further studies are needed to elucidate the potential role of the INI1 protein on development of the rhabdoid phenotype in patients with these highly aggressive brain tumors.

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DISCLOSURE

The authors have no conflict of interest associated with this article.

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