NEUROPATHOLOGY

Neuropathology 2011; **31**, 421–426 doi:10.1111/j.1440-1789.2010.01166.x

Case Report

Rhabdoid glioblastoma: Case report and literature review

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Rhabdoid glioblastoma is a recently described entity in which a glioblastoma is associated with a rhabdoid component. Although rhabdoid glioblastoma has not appeared in the new World Health Organization classification of tumors of the CNS, it has a specific morphological feature and highly aggressive clinic process. Up to now, there have been six cases of rhabdoid glioblastoma reported in the literature. We report rhabdoid glioblastoma in the right front temporal lobe from a 31-year-old Chinese man. This tumor consisted of rhabdoid tumor cells with an eccentric nucleus and an eosinophilic cytoplasm. The tumor had an area appearing to be glioblastoma with microvascular proliferation and necrosis, and lacked a primitive neuroectodermal tumor component, and a mesenchymal component. Vimentin, epithelial membrane antigen, GFAP and integrase interactor (INI-1) expression were found in the tumor cells. Genetic abnormalities which include monosomy or a deletion of chromosome 22 were not found in this tumor. After 3 months post-surgery, the tumor was widespread in leptomeningia and the patient died. In conclusion, rhabdoid glioblastoma is a rare glioblastoma with poor prognosis; the differential diagnosis contained other rhabdoid tumors. This case will contribute to the profile of rhabdoid glioblastoma with typical morphology and immunophenotype, genetic and clinic features.

Key words: clinicopathological feature, differential diagnosis, glioblastoma, prognosis, rhabdoid.

INTRODUCTION

Rhabdoid tumor is characterized by large, morphologically monomorphous and relatively noncohesive rhabdoid cells.[1–8] It was first described as one subtype of Wilms' tumors of the kidney, presenting with rhabdomyosarcomatoid features.[1,9] However, the cells of rhabdoid tumor were found ultrastructurally not to differentiate into rhabdomyoblasts and immunohistochemically negative to desmin and myogenin.[3] In addition to the kidney, rhabdoid tumors have been reported to arise from other organs such as the CNS, liver, soft tissues of the head and neck, mediastinum, retroperitoneum, pelvis and skin.[10] Atypical teratoid/rhabdoid tumor (AT/RT) is a representative tumor with rhabdoid cells in the CNS,[2,3] which usually arises in young children and with a highly aggressive process. Besides AT/RT, a supratentorial rhabdoid tumor, containing regions of glioblastoma, was reported and designated as rhabdoid glioblastoma.[4–8] This tumor had a specific rhabdoid morphological feature and poor prognosis.

Here, we present a case of rhabdoid glioblastoma in the right front temporal lobe in a 31-year-old Chinese man with typical morphology and immunophenotype, genetic and clinic features.

CASE REPORT

A 31-year-old Chinese man presented with a head injury and forehead headache of 15 days duration. There was no significant past medical history. On examination he did not have any focal neurological deficits. The CT scan showed a mass with size 5 cm × 4.5 cm in the right front temporal lobe near to the lateral ventricle with peripheral calcification (Fig. 1A). MRI showed a tumor in the right front temporal lobe and the right lateral ventricle was compressed. T1-weighted images showed the tumor to be of mixed signal intensity (Fig. 1B) and on T2-weighted images there was edema surrounding the lesion with an uneven

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Conflicts of interest: none.

Received 5 July 2010; revised and accepted 2 September 2010; published online 24 November 2010.

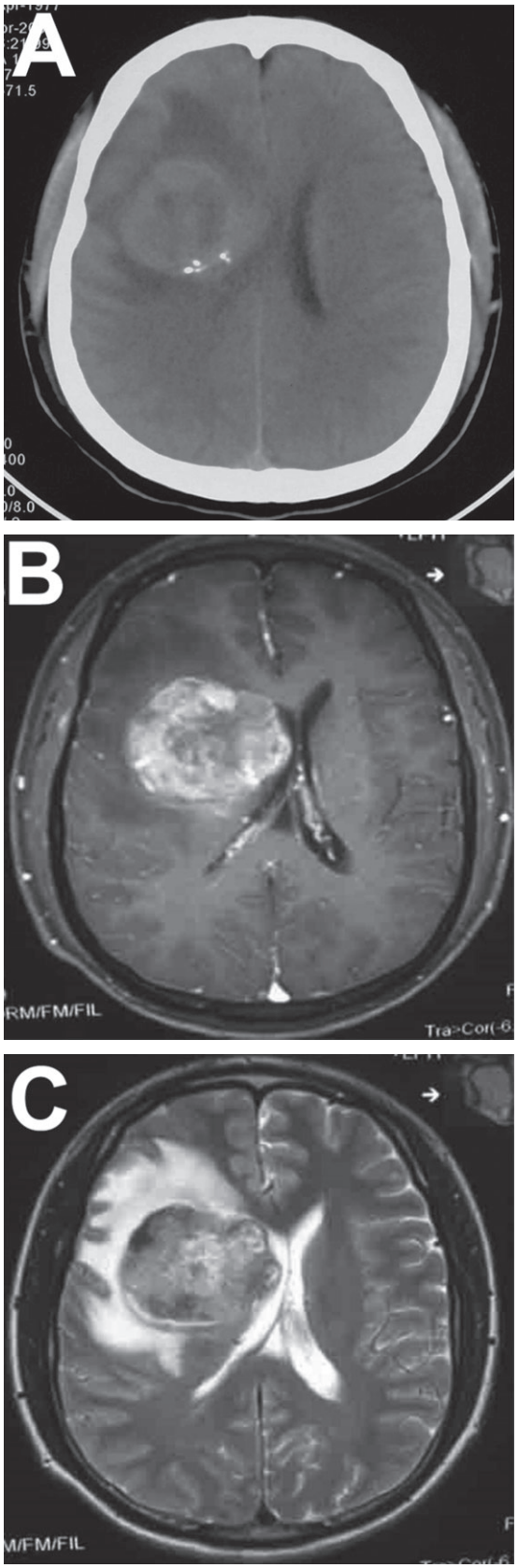

Fig. 1 CT scan showing a mass with size 5 cm × 4.5 cm in the right front temporal lobe near to the ventricle with peripheral calcification (A). MRI showing a well-circumscribed tumor in the front temporal lobe near the right lateral ventricle. T1-weighted images show the tumour to be of mixed signal intensity (B). T2 weighted images show edema surrounding the lesion with an uneven contrast enhancement (C).

contrast enhancement (Fig. 1C). Under surgery, the tumor was found approximately 1 cm into the subcortex and was sized 4 cm × 3 cm × 3 cm. The right lateral ventricle was involved and the surrounding brain parenchyma was compressed by the tumor. The superficial margin between the tumor and the brain parenchyma was distinct and the main portion of the tumor was gray and soft. The patient was treated with a right front temporal craniotomy and excision of the tumor.

The patient underwent postoperative chemotherapy. CT scan 1 month post-operatively showed no evidence of recurrent or residual disease. However, 3 months after the operation he developed headaches and lethargy. MRI of the brain and spine showed evidence of widespread leptomeningeal disease. Chemotherapy and spinal radiotherapy were offered but he died a week later. Autopsy was not performed.

NEUROPATHOLOGICAL FINDINGS

Histopathological findings

Histopathology revealed a high-grade pleomorphic malignant tumor containing areas of infiltrating malignant astrocytoma with neocrosis and microvascular proliferation. Processes of these tumor cells were prominent and formed a loose fibrillary matrix, with focal to sheet fiber fibrillary hyperplasia (Fig. 2A).These features corresponded to those of glioblastoma. There were other areas of tumour cells morphologically consistent with those of rhabdoid cells. The rhabdoid tumour cells were characterized by vesicular eccentric nuclei with prominent nucleoli and abundant eosinophilic cytoplasm containing inclusion bodies (Fig. 2B). A transitional zone from this part to the glioblastoma was also observed. Mitotic figures were easily observed in both areas. This tumor lacked a primitive neuroectodermal tumor component. A mesenchymal component and morphological epithelial differentiation were not observed in the tumor.

Immunohistochemistry

Immunohistochemistry was performed on formalin-fixed and paraffin-embedded sections using monoclonal antibodies vimentin, GFAP, epithelial membrane antigen

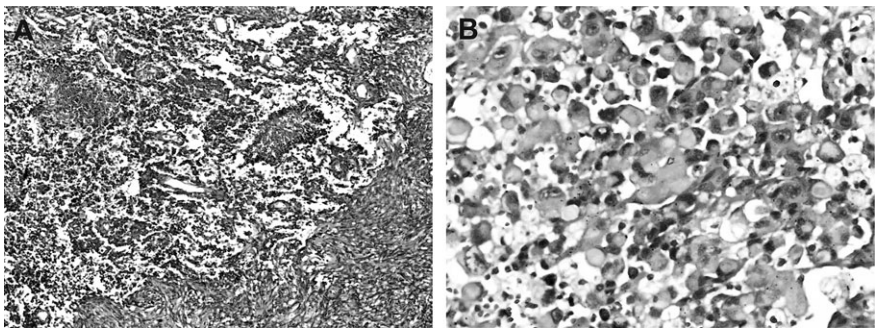

Fig. 2 Histopathological findings. The resection specimen showed a high-grade pleomorphic malignant tumour containing areas of infiltrating malignant astrocytoma with neocrosis and microvascular proliferation. The processes of these cells were prominent and formed a loose fibrillary matrix, with plenty of focal to sheet fibrillary hyperplasias. (A, HE staining, ×100). There were other areas of rhabdoid tumor cells characterized by vesicular eccentric nuclei with prominent nucleoli and abundant eosinophilic cytoplasms containing inclusion bodies. (B, HE staining, ×400).

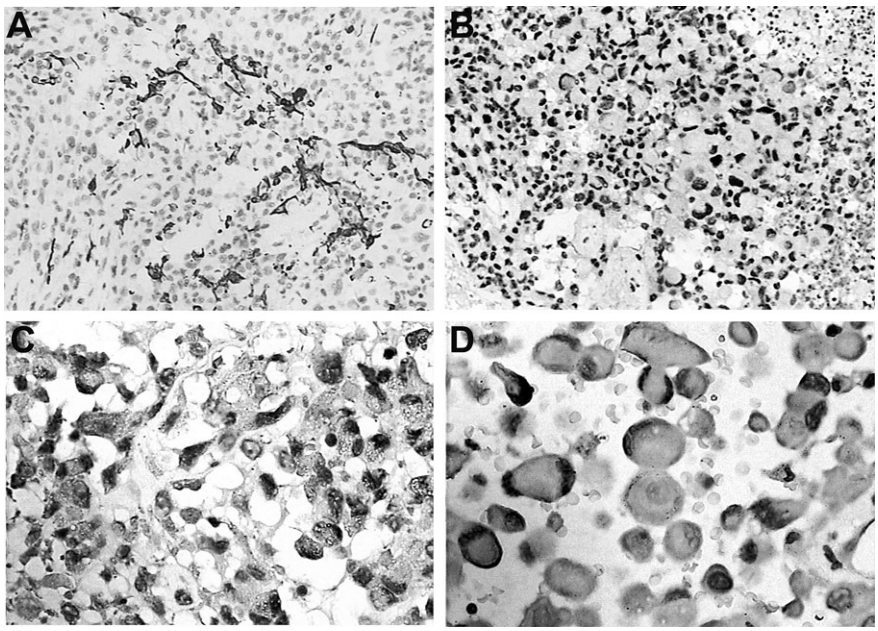

Fig. 3 Immunohistochemical findings. GFAP and INI-1 were expressed in tumor cells (A, anti-GFAP ×200; B, anti-INI-1 ×200); The vimentin and epithelial membrane antigen (EMA) were diffusely positive in tumor cells of rhabdoid glioblastoma (C, anti-vimentin ×400; D, anti-EMA ×400).

(EMA), α-smooth-muscle actin (SMA), S-100 protein, desmin and myogenin, CD99, synaptophysin (Syn), P53 and ki-67. INI-1 protein, the hSNF5/INI-1 tumor suppressor gene product, was specially observed in tumor cells. The germ cell markers of alpha fetoprotein (AFP), placental alkaline phosphatase (PLAP) and human chorionic gonadotrophin (HCG) were also analyzed. The primary antibodies and immunohistochemistry staining kits were EnVision Plus system (Dako Corporation, Glostrup Denmark). The specimen underwent performed reticular fiber staining as routine.

Immunohistochemically, a subpopulation of the tumour was unequivocally GFAP immunopositive (Fig. 3A). In particular, staining for INI-1, the hSNF5/INI-1 tumor suppressor gene product, was positive in the tumor cells (Fig. 3B). Almost all tumor cells were positive with vimentin (Fig. 3C), and tumor cells with the rhabdoid cells showed strong immunostaining with EMA (Fig. 3D) but immunonegative for desmin and myogenin. A few tumor cells weakly expressed SMA and S-100 protein. p53 had accumulated in the nuclei of the tumor cells. The MIB-1 labeling index of the tumor cells was 8%. In this case, there was no evidence of primitive neuroectodermal tumour (PNET) in the morphology and the tumor cells were negative to Syn and CD99. The germ cell markers of AFP, PLAP and HCG were also all negative. Reticular fiber staining in the area of fibrillary hyperplasia was negative.

Cytogenetic anlysis

Karyotype analyses were prepared from fresh tumor specimens and chromosomes were harvested. The tumor was demonstrated without monosomy 22 or deletion as apparently normal chromosome 22.

DISCUSSION

Rhabdoid phenotypic change has been described in a number of different neoplasms from many organs.[1,9,10]

These tumors share common morphologic and electron-microscopic features, polyphenotypic immunohistochemical profile and cytogenetic abnormalities of chromosome 22.[1,9] The term "rhabdoid" was coined because the tumour cells show eosinophilic cytoplasm-simulating rhabdomyoblasts but the ultrastructural and immunohistochemical findings do not support a muscle origin.[11] The histogenesis of the rhabdoid cell is unknown.[3,11,12] Although rhabdoid cells are referred to as neoplastic cells containing tight cytoplasmic inclusions of filaments that are immunoreactive for vimentin, they are not true rhabdomyoblasts or have muscle origins.[7,8]

Atypical teratoid/rhabdoid tumor is the common rhabdoid tumor in the CNS and is associated with a PNET component.[2,3] Other rhabdoid tumors of the CNS are rare, including rhabdoid meningiomas[13] and malignant rhabdoid tumors of uncertain histogenesis.[10,14] Rhabdoid glioblastoma is a recently described entity associated with a rhabdoid component. Here we have detailed a case of an aggressive rhabdoid tumor in the right frontal lobe from a 31-year-old Chinese man, which was associated with glioblastoma and no areas of PNET were identified. There were prominent rhabdoid tumor cells in this case. Immunohistochemistry showed that the tumour cells with rhabdoid phenotype were positive for vimentin, EMA and INI-1, but negative for desmin and myogenin. The glial component of the tumour cells showed positive for GFAP. The cytogenetic studies demonstrated without monosomy or deletion of chromosome 22. The present case documents progressive rhabdoid transformation of a glioblastoma (Table 1).

Although rhabdoid glioblastoma has not appeared in the World Health Organization classification of tumors of the CNS,[3] it has specific morphological features and is highly aggressive with possible recurrence and metastases. In 2001, Wyatt-Ashmead *et al*. reported a rhabdoid tumor admixed with an area of low-grade glioma.[4] There was a region of glioblastoma multiforme. The rhabdoid cells appeared to have arisen from the region of a low-grade glioma with secondary phenotypic change, thus they designated this tumor as rhabdoid glioblastoma. Subsequently, two other similar rhabdoid tumors with regions of high-grade astrocytoma were reported and also designated as rhabdoid glioblastoma.[5,6] In 2009, Nagai and colleagues also reported a rhabdoid tumor admixed with an area appearing to be diffuse astrocytoma peripherally and lacked a primitive neuroectodermal tumor component, a mesenchymal component and epithelial differentiation.[7] The tumor cells had INI expression and they concluded that this tumor was an astrocytic tumor with rhabdoid features, and thought the tumor cells exhibiting rhabdoid features had secondarily arisen from the peripheral area, presenting an appearance of diffuse astrocytoma. Then Kleinschmidt-DeMasters

Table 1 Clinicopathological and immunohistochemical features of rhabdoid glioblastoma from the literature

Patient age/gender	Location	Morphology	Phenotype	Survival (weeks)	Authors
1 18/M	Right frontal lobe	Rhabdoid cells Epithelial cells Necrosis Vascular	Vim+, EMA+ S100+, GFAP focal+	20	Wyatt-Ashmead *et al*. (2001)[4]
2 16/F	Right medial Temporal lobe	Rhabdoid cells Epithelial cells Necrosis	Vim+, EMA+ SMA+, GFAP focal+	12	Lath *et al*. (2003)[5]
3 66/M	Right temporal lobe	Rhabdoid cells Giant cells Necrosis	Vim+, EMA+ SMA+, GFAP +	1	Fung *et al*. (2004)[6]
4 18/M	Left temporal lobe	Rhabdoid cells Diffuse astrocytoma	Vim+, EMA+ SMA+, GFAP +, INI-1+	3	Nagai *et al*. (2009)[8]
5 18/M	Right frontal lobe	Rhabdoid cells Atypical astrocytes	EMA+, INI-1+ P53+, GFAP focal +, Claudin-6–	22	Kleinschmidt-DeMasters *et al*. (2010)[7]
6 67/F	Right frontal lobe	Rhabdoid cells Atypical astrocytes, Vascular	EMA+, INI-1+ EGFR+, GFAP focal+, Claudin-6-	36	Kleinschmidt-DeMasters *et al*. (2010)[7]
7 31/M	Right frontal lobe	Rhabdoid cells Atypical astrocytes, Necrosis Vascular	Vim+, EMA+ P53+, INI-1+, GFAP focal+ Syn–	12	He *et al* (This report)

Vim, vimentin; EMA, epithelial membrane antigen; SMA, α-smooth-muscle actin; Syn, synaptophysin.

et al. analyzed the immunphenotype of two cases of rhabdoid glioblastoma and thought that INI-1 and Claudin-6 were useful in distinguishing AT/RT from rhabdoid glioblastoma, and not useful in distinguishing rhabdoid glioblastoma from epithelioid glioblastoma.[8] In their two cases of rhabdoid glioblastoma, there was retention of immunostaining for INI-1 in the glioblastoma cells that lacked rhabdoid features, but loss in a subset of the cells with the most rhabdoid features in one case. In our case, although the tumor cells with eosinophilic cytoplasm and eccentric nuclei, which were diffusely positive for vimentin and EMA, there was a typical rhabdoid glioblastoma which contained rhabdoid cells and areas of infiltrating malignant astrocytoma with neocrosis and microvascular proliferation. According to Kleinschmidt-DeMasters *et al*.'s description,[8] we thought our case was rhabdoid glioblastoma with epithelial differentiation.

Almost all rhabdoid glioblastomas including the present case were located supratentorially or in the subcortex. Most cases were young patients with median age of approximately 17 years. Our patient was 31 years old, and there are two other older patients (66 and 67 years old) in the literature. Rhabdoid glioblastoma morphologically contains a glioblastoma component and rhabdoid tumor cells. Ultrastructurally, rhabdoid cells do not show evidence of muscle origin differentiation. The rhabdoid cells have a broad immunohistochemical profile. They almost always express EMA and vimentin. Expression of SMA of CD99 is not consistent. They may also express GFAP, S100 protein and keratin but do not express desmin and myogenein. These tumor cells do not express the phenotype of PNET, such as synaptophysin or any of the markers of AFP, PLAP and HCG for germ cell tumours.[1–4] When rhabdoid phenotypic change is present in a primary brain tumour like glioblastoma, the parent tumor has its own specific immunohistochemistry, where the tumor cells in the glial component showed immunopositivity for GFAP. Expression of INI, the hSNF5/INI-1 tumor suppressor gene product negative in AT/RT, was always found in this tumor, and is considered a useful phenotype for diagnosis. INI positivity in tumor cells indicates that homozygous inactivation of the hSNF5/INI-1 gene has not occurred in the tumor cells with rhabdoid features. Kleinschmidt-DeMasters *et al*. thought that their one of two cases of rhabdoid glioblastoma which had focal loss of INI-1 protein expression may represent a second genetic hit in the INI-1 gene in a subset of the tumor cells. This second hit would be occurring in an astrocytic neoplasm that already possesses background monosomy 22.[8] Genetic abnormalities, including monosomy or deletion of chromosome 22, are well described in AT/RT, but are mostly negative in rhabdoid glioblastoma.[4–8] There were exclusions with monosomy 22 in two cases of rhabdoid glioblastoma reported by Kleinschmidt-DeMasters *et al*. and one case of rhabdoid glioblastoma reported by Wyatt-Ashmead.[4]

The differential diagnosis of rhabdoid glioblastoma contained other rhabdoid tumors. The radiological features of rhabdoid glioblastoma and atypical teratoid/rhabdoid tumors are non-specific.[2–8] On unenhanced CT scans these tumors are hyperdense and show inhomogenous contrast enhancement. On MRI they are iso- to hypointense on T1-weighted images and are of mixed signal intensity on T2-weighted images and enhance with gadolinium. Cystic, hemorrhagic, calcific and necrotic foci may be present.[3,14,15] Morphologically, rhabdoid glioblastoma presenting with rhabdoid features with areas appearing to be glioblasoma, lack a primitive neuroectodermal tumor component and a mesenchymal component which are specifically found in AT/RT.[2,3] INI expression, which is not observed in AT/RT, is always found in rhabdoid glioblastoma.[2,3,16] AT/RT have been well as described genetic abnormalities which include monosomy or a deletion of chromosome 22, and are mostly negative in rhabdoid glioblastoma. From these features, rhabdoid glioblastoma has been easily differentiated from AT/RT.[16–18] In addition, Kleinschmidt-DeMasters *et al*. thought Claudin-6 was useful in distinguishing AT/RT from rhabdoid glioblastoma. As to other rhabdoid tumors in the CNS, such as rhabdoid meningiomas and malignant rhabdoid tumors of uncertain histogenesis, these tumors have areas of glioblastoma and are positive for GFAP, which may help differentiate the tumor from other rhabdoid tumors.[10,17–19] In our case, the tumor tissue had plenty of focal to sheet fibrillary hyperplasias, which are easily misdiagnosed as gliosarcoma. Considering the tumor cells in our case case formed a loose fibrillary matrix, we performed reticular fiber staining in the area of fibrillary hyperplasia. The reticular fiber staining was negative and there was no apparent fibrosarcoma component in this case, thus gliosarcoma could be excluded.[3]

Rhabdoid glioblastoma is a highly aggressive tumour with poor prognosis. The tumor has been reported with a potential for early recurrence, leptomeningeal spread and extracranial metastases.[4–8] The treatment includes surgery, cranial or cranio-spinal radiation and multi-agent chemotherapy in various combinations, similar to conventional glioblastoma. The outcome with this tumor is poor and survival in previously reported cases of rhabdoid glioblastoma was 5 months despite repeated surgery, chemotherapy and radiation.[4–8,20] The patient in our case underwent post-operative chemotherapy, and widespread leptomeningeal development occurred 3 months after the operation. Although chemotherapy and spinal radiotherapy were offered, he died a week later. It is still not clear whether rhabdoid glioblastomas should be treated like other malignant rhabdoid tumors with surgery followed by aggressive multi-agent chemotherapy and cranio-

spinal radiation, or like high-grade gliomas. Thus, the treatment of rhabdoid glioblastoma required the accumulation of more clinical data and therapy experience.

In conclusion, the rhabdoid glioblastoma is a rare glioblastoma with specific rhabdoid tumor cells and a highly aggressive clinical process and poor prognosis. The differential diagnosis contains any other rhabdoid tumors such as AT/RT and so on. This case will contribute to the profile of rhabdoid glioblastoma with typical morphology and immunophenotype, genetic and clinic features.

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