Cerebral Medulloepithelioma With Long Survival

—Case Report—

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Abstract

An 8-year-old boy presented with a rare cerebral medulloepithelioma manifesting as headache, nausea, and vomiting. Neuroimaging demonstrated a mass containing a cyst in the left frontal lobe. Gross total resection of the tumor with a 1-cm margin was performed under intraoperative monitoring. The histological diagnosis was medulloepithelioma. Stereotactic radiotherapy (total dose 20 Gy) was given to the brain up to 1 cm from the surgical margin. Follow-up neuroimaging 5 years later showed no signs of recurrence. He now attends junior high school, with normal mental and physiological development. Medulloepitheliomas are rare, highly malignant embryonal tumors of the central nervous system. Combined gross total tumor resection and radiotherapy are recommended to obtain the most favorable outcome.

Key words: medulloepithelioma, cerebrum, prognosis, surgery, radiation

Introduction

Medulloepitheliomas, first described by Bailey and Cushing in 1926,²⁾ are rare, highly malignant primitive neuroectodermal tumors usually occurring in childhood. Histologically, they resemble the primitive medullary plate and neural tube.^{2,28,35)} The most common site is periventricular within the temporal, parietal, and frontal lobes, in that order.^{9,11,13,21,22,44,45,47)} These neoplasms are believed to arise from primitive undifferentiated matrix cells around the periventricular area.³⁵⁾ The high rate of recurrence due to rapid subarachnoid spread and radioresistance of the tumor cells results in a poor prognosis with overall median survival of 5 months.^{1,3,4,6,9,11,13,21,22,25,28,32,35,38,43-45,47)} Long-term survivors had undergone gross total resection.^{25,28,46)}

We report a case of medulloepithelioma with long-term survival of more than 6 years in a 13-year-old boy treated by gross total resection and removal of the surrounding brain tissue infiltrated by tumor cells.

Case Report

An 8-year-old boy was admitted to our hospital because of headache, nausea, and vomiting in March 2000. Neurological examination on admission showed bilateral papilledema. Routine hematological study disclosed no abnormalities. Computed tomography (CT) revealed a well-circumscribed heterogeneous isodense mass containing a cyst in the left frontal lobe, with heterogeneous enhancement with contrast medium (Fig. 1). T₁-weighted magnetic resonance (MR) imaging showed an isointense mass, heterogeneously enhanced with gadolinium-diethylenetriaminepenta-acetic acid (Gd-DTPA), containing a cystic component, and hyperintense areas suggestive of intratumoral hemorrhage (Fig. 2). The preoperative diagnosis was anaplastic ependymoma.

Left frontotemporal craniotomy exposed the reddish tumor which was well demarcated from the adjacent brain (Fig. 3). The tumor was soft and contained a cyst with bloody fluid. The tumor was totally removed after coagulation of the adhering falx. In addition, the surrounding brain was excised to a depth of 1 cm from the margin of the tumor cavity because intraoperative histological study of

Fig. 1 Computed tomography scans showing a mixed density mass in the left frontal lobe (A), and heterogeneous enhancement of part of the tumor with contrast medium (B).

Fig. 2 T₁-weighted magnetic resonance images showing a well-circumscribed heterogeneous mass with hyperintense areas suggestive of hemorrhage (A), and heterogeneous enhancement of the mass by gadolinium (B).

Fig. 3 Intraoperative photograph showing a mass well demarcated from the surrounding brain. The tumor adhered to the falx (arrows).

Fig. 4 Photomicrographs of the tumor showing neural tube-like structures with a pseudo-stratified epithelium and internal and external limiting membrane (A: hematoxylin and eosin [HE] stain, original magnification $\times 400$), mitoses near the internal limiting membrane (B: HE stain, original magnification $\times 400$), rosette formation with the central lumen (C) and choroid plexus elements (D) (C, D: HE stain, original magnification $\times 400$), tumor cells infiltrating into the adjacent parenchyma (E: HE stain, original magnification $\times 200$), and positive immunohistochemical staining for AE1/AE3 at the luminal border of the neural tube-like structures (F: original magnification $\times 400$).

frozen sections showed infiltration by tumor cells. Intraoperative monitoring of motor evoked potential^[20,41] and somatosensory evoked potential showed no changes during resection of the tumor and surrounding brain.

Histological examination found various neural tube-like tubular, capillary, and trabecular structures composed of pseudo-stratified primitive neuroepithelium (Fig. 4A, B). These structures were clearly separated from each other by a basement membrane positive for periodic acid-Schiff staining. The pattern-less cellular areas contained many immature rosette-like structures (Fig. 4C). Vascular proliferation necrosis and calcification were com-

mon. Foci of choroid plexus-like configurations were also observed (Fig. 4D). Tumor cells had infiltrated into the surrounding brain tissue (Fig. 4E). The neural tube-like structures were immunopositive for cytokeratin (AE1/AE3) (Fig. 4F), and the undifferentiated areas were positive for glial fibrillary acidic protein and synaptophysin staining. There was no immunoreactivity for epithelial membrane antigen, collagen type IV, alpha-fetoprotein, or carcinoembryonic antigen. The MIB-1 index for proliferative activity was 41.8% for tumor cells in highly cellular portions and 15.5% for those in other overlying areas.

His postoperative course was uneventful and the symptoms attributable to hypertensive intracranial pressure were resolved. He manifested no neurological deficits. The area up to 1 cm from the surgical margin was treated with stereotactic radiotherapy (total dose 20 Gy). MR imaging obtained 5 years after the operation detected no residual tumor or recurrence. At present, the patient attends junior high school, and his mental and physiological development is normal.

Discussion

Approximately 50 cases of medulloepithelioma have been reported (Table 1).^{1-19,21-40,42-45} Although most medulloepitheliomas manifest in the first decade of life,^{1,11,13,15,22,25,28,31,39,40,44} they are occasionally found in patients older than 20 years.^{25,38} These tumors tend to be fatal despite treatment by surgery and/or irradiation and/or chemotherapy.^{1,6,10,11,21,22,28,31,38,40,44} On the other hand, intraorbital,^{7,8,15,30} peripheral,²⁶ and cauda equina²² medulloepitheliomas have a much less malignant course and even those treated primarily or only by enucleation tend not to recur for a long time.^{7,15,19,27} Extracranial and intracranial medulloepitheliomas have similar histological features,^{8,30} and the great difference in the prognosis remains to be elucidated. In addition, the differences in the biological characteristics and behaviors of these neoplasms are unexplained.

Medulloepithelioma mimics the primitive neural tube and tends to exhibit differentiation into neuronal, glial, and mesenchymal elements.³⁹ Approximately 50% of the reported tumors had the potential for differentiation into astroglial, ependymal, or neuronal cell lines,^{1,4,21,22,38} and some into mesenchymal cell lines.¹ Central nervous system cytogenesis occurs in three stages: in the first mitotic phase the matrix cell population is increased, in the second stage the matrix cells begin to differentiate into neuroblasts that migrate outward to form the mantle layer, and in the third stage the matrix cells develop

into glioblasts, i.e. precursors of astrocytes and oligodendrocytes.¹⁴ The glioblasts rapidly migrate outward and retain their mitotic activity. Cells remaining near the lumen of the neural tube develop the features of differentiated ependymal cells. Glial cell differentiation occurs during the third stage of cytogenesis.²¹ Ependymal differentiation is suggested by cytokeratin reactivity at the luminal surface, indicating the maturation of residual germinative cells located next to the lumen of the original neural tube, also occurring in the third stage.⁴⁶

The present tumor exhibited some features of ependymal and choroid plexus differentiation. Moreover, some of the internal and external limiting membranes were immunopositive for AE1/AE3. These findings correspond with the third stage of cytogenesis. The present tumor was also immunoreactive for vimentin, the first intermediate filament protein demonstrated in the early developmental stage of the mammalian neural tube.^{6,36} Medulloepitheliomas may express all stages of central neurogenic maturation, from the most embryonal to the most differentiated cell types, in a single tumor. It remains unknown why in some cases the neural tube becomes a malignant tumor and why some individuals develop medulloepitheliomas after birth. These tumors may derive from neural tube-like tissue either as a result of neoplastic transformation at some stage of fetal or early postnatal development^{11,32,43} or from the anomalous gene re-expression of early neural tube determinants.^{24,46}

Medulloepitheliomas at initial presentation generally appear as well circumscribed, iso- to slightly hypodense neoplasms on CT scans,^{28,31} and as hypo- or hyperintense tumors on T₁- and T₂-weighted MR images. Medulloepitheliomas are typically not enhanced by contrast medium on CT and MR imaging,²⁶ but our case showed heterogeneous enhancement with iodinated contrast medium and Gd-DTPA. This finding may reflect the more aggressive nature of these tumors at recurrence.²⁸ Histological findings of tumor infiltration into adjacent brain tissue and high MIB-1 index are suggestive of tumor progression. Therefore, tumor cell infiltration into the adjacent brain tissue should be evaluated intraoperatively by histological analysis of frozen sections in patients with CT and/or MR imaging findings indicating tumor progression.

Only four long-term survivors have been reported, all treated by gross total tumor removal (Table 1).^{25,28,46} Two of eight patients with central nervous system medulloepithelioma achieved long-term survival without recurrence.²⁸ One patient underwent gross total resection and the other

Table 1 Literature reports of intracranial medulloepitheliomas that have available information on location, surgery, and outcome

Case No.	Author (Year)	Age	Location	Surgery	Radiation	Chemotherapy	Survival
1	Treip (1957) ^{43]}	9 days	midbrain/cerebellum	none	none	none	8 mos
2	Fujita (1965) ^{14]}	1 yr 10 mos	hypothalamus	none	none	none	8 mos
3	Van Epps et al. (1967) ^{45]}	5 yrs	temporal	PR	45.6 Gy	NR	6 mos
4	Fowler (1968) ^{13]}	3 yrs 2 mos	cerebral hemisphere	PR	none	none	5 mos
5	Deck (1969) ^{11]}	1 yr 4 mos	parietal	GTR	none	none	death ¹
6	Jellinger (1972) ^{21]}	7 mos	temporoparietal	GTR	none	none	9 mos
7	Karch and Urich (1972) ^{22]}	3 yrs	parietal	PR	none	none	4 mos
8		2 yrs	temporal	biopsy	41 Gy, 41 Gy for spine	none	5 mos
9	Lolova et al. (1972) ^{25]}	23 yrs	frontotemporal	GTR	yes*	none	>4 yrs
10	Best (1974) ^{3]}	2 yrs	cerebellum	biopsy	none	none	2 wks
11	Pollak and Friede (1977) ^{32]}	15 mos	cerebellum	PR	yes*	none	11 mos
12	Scheithauer and Rubinstein (1979) ^{38]}	12 yrs	thalamus	none	50 Gy, 15 Gy for tumor field	CCNU, VN-26	2 yrs 11 mos
13	Sato et al. (1980) ^{37]}	1 mo	cerebellum	none	none	NR	<1 mo
14	Auer and Becker (1983) ^{1]}	2 yrs 6 mos	parietooccipital	PR	53 Gy	none	11 mos
15	Bonnin et al. (1984) ^{4]}	15 mos	cerebellum	yes*	none	none	4 mos
16	Troost et al. (1990) ^{44]}	3 yrs	parietooccipital	PR	none	none	3 mos
17	Molloy et al. (1996) ^{28]}	4 yrs 4 mos	pons	shunt	local 72 Gy	thiopeta (four cycles), ABMT	1 yr 8 mos
18		3 yrs	pons	none	local 72 Gy	none	1 yr 11 mos
19		1 yr 3 mos	cerebellum	GTR	26 Gy, local 20 Gy	intrathecal MTX	>13 yrs 5 mos
20		1 yr	third ventricle, thalamus, posterior fossa, temporal	biopsy	none	none	3 mos
21		2 yrs 8 mos	frontal	GTR	28 Gy, local 25.2 Gy	VCR, CDDP, CCNU	10 mos
22		1 yr 5 mos	temporoparietal	GTR	55 Gy	VCR, VP-16, CDDP, CPM, CARBO, ABMT	>3 yrs 8 mos
23		6 mos	fourth ventricle, cerebellum	ventriculostomy	none	none	3 days
24		3 yrs	thalamus	PR	none	VP-16, CPM, CARBO	10 mos
25	Khoddami and Becker (1997) ^{24]}	2 yrs 6 mos	cerebrum	PR	yes	none	11 mos
26		2 yrs 6 mos	cerebrum	PR	yes	none	death ³
27		35 wks ges	posterior fossa	VP shunt	none	none	6 days
28	Sharma et al. (1998) ^{39]}	9 mos	fourth ventricle	GTR	none	none	death ²
29	Pang et al. (2001) ^{31]}	2 yrs	suprasellar	PR	none	VCR, CPM, CDDP, VP-16	2 yrs
30	Vincent et al. (2002) ^{46]}	3 mos	fourth ventricle	GTR	none	none	>7 yrs
31	Sundaram et al. (2003) ^{40]}	3 yrs	parietotemporo-occipital	biopsy	none	none	death ⁴
32	Present case	8 yrs	frontal	GTR	20 Gy (surrounding brain)	none	>6 yrs

ABMT: autologous bone marrow transplant with etoposide (VP-16)/cyclophosphamide (CPM)/thiopeta/cytoreduction, CARBO: carboplatinum, CCNU: 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, CDDP: cis-diamminedichloroplatinum, death¹: cardiac arrest after surgery, death²: pulmonary infection 2 weeks after surgery, death³: died at home, death⁴: perioperative period, ges: gestation, GTR: gross total resection, MTX: methotrexate, NR: not recorded, PR: partial resection, VCR: vincristine, VN-26: teniposide, VP: ventriculoperitoneal, yes*: no detailed information.

second gross total resection for tumor recurrence. The absence of tumor cell infiltration and gross total resection probably contributed to the prolonged survival. Our patient had a favorable outcome, despite intraoperatively confirmed tumor cell infiltration into the surrounding brain tissue. We extended resection to the surrounding brain with no evidence of tumor cells. We recommend that in the presence of tumor cell invasion into the surrounding brain, resection should include the tissue with tumor cell infiltration. Intraoperative histological examination of frozen sections is essential to determine the extent of radical resection required and helps to confirm complete removal of invaded tissue.

The efficacy of adjuvant therapy including irradiation and chemotherapy is controversial.²⁸⁾ Four of the five long-term survivors, including ours, received postoperative radiotherapy.^{25,28)} We treated our patient with stereotactic radiotherapy after gross total tumor resection because of the danger of intellectual impairment in young children exposed to whole-brain irradiation.⁷⁾ Two of the five operated patients with favorable treatment outcome^{25,28,46)} were also treated with chemotherapy, and one received autologous bone marrow transplantation.²⁸⁾ The effectiveness of aggressive chemotherapy and autologous bone marrow transplantation remains to be determined.

To achieve long-term favorable outcomes in patients with cerebral medulloepitheliomas, we recommend gross total tumor resection and excision of any surrounding brain tissue infiltrated by tumor cells.

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