VIII. 9. Static Progression of Pediatric Malignant Brain Tumors with Metastases


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**Introduction**

Metastasis and dissemination are the major causes of tumor related deaths. It is reported that both non-proliferating tumor cells and non-angiogenic micrometastases can remain dormant and occult for months or years, called dormancy in metastasis\(^1,\)\(^2\). However, once these dormant micrometastases turn to macrometastases and show progressive growth, they shortly become lethal. There are few reports that clinically apparent macrometastases can remain static for a long period in pediatric malignant brain tumors.

In this article, we report three cases of pediatric malignant brain tumors which have macrometastases. In all cases, these metastatic lesions remain static for a long period after the initial treatments. We also attempt to use \(^{11}\)C-methionine-positron emission tomography (MET-PET) to elucidate the metabolic activities in these clinically static metastatic lesions.

**Case descriptions**

**Case 1**

A 1-year-old boy was admitted to our department with an enlarged head circumference in August 1998. Magnetic resonance (MR) images demonstrated a mass lesion in the cerebellar vermis (Fig. 1a). The lesion was completely removed via a cerebellomedullary fissure approach, and the tumor was histologically diagnosed as desmoplastic medulloblastoma. Postoperatively, he received three cycles of combination chemotherapy using cisplatin and etoposide (PE chemotherapy). Although he had showed no neurological deterioration, T1-weighted MR imaging with gadolinium-diethylenetriaminepenta-acetic acid (Gd-DTPA), obtained in February 1999,
revealed multiple enhanced lesions in the bilateral cerebellar hemisphere, vermis, bilateral cerebral hemisphere, and spinal cord at the level of Th1 (Fig. 1b). These lesions were diagnosed as disseminated recurrence, and he received six additional cycles of PE chemotherapy. MR imaging in October 1999 demonstrated the new disseminated lesions in the medulla oblongata, left temporal lobe, left cerebellar hemisphere, and spinal cord at the level of C2 and C5, although other disseminated lesions showed no remarkable changes. He received irradiation consisting of 24 Gy to the whole brain and spinal cord, and 30 Gy to the posterior fossa, followed by four courses of chemotherapy using ifosfamide, cisplatin, and etoposide (ICE chemotherapy). Serial MR imaging had showed no obvious changes in the enhanced lesions for six years. However, MET-PET in June 2007 indicated that the enhanced lesion in the cerebellar vermis had elevated uptake of $^{11}$C-methionine in which the maximum standardized uptake value ($SUV_{\text{max}}$) was 3.0 (Fig. 2a). MR imaging obtained in August 2007 demonstrated slight enlargement of the lesions. His current modified Rankin scare score is 5 after he received seven cycles of temozolomide chemotherapy.

**Case 2**

A 4-year old boy was admitted to our department presenting with headache. T1-weighted MR images with Gd-DTPA of the brain and spinal cord demonstrated a heterogeneously enhanced mass lesion in the cerebellar vermis (Fig. 1c) and nonenhanced intramedullary hypointensity lesion from C5 to Th1. The lesion in the cerebellar vermis was completely removed via a cerebellomedullary fissure approach, and the tumor was histologically diagnosed as medulloblastoma. Postoperatively, he received three courses of PE chemotherapy followed by irradiation consisting of 24 Gy to the whole brain and spinal cord, and 30 Gy to the posterior fossa. Three more courses of PE chemotherapy were given subsequently. The tumor in the cervical spinal cord slowly expanded during the four years. Serial MET-PET indicated progressive elevated uptake in the spinal cord lesion, in which the mean of SUV ($SUV_{\text{mean}}$) was 1.62 in July 2003 (Fig. 2b), and $SUV_{\text{mean}}$ was 2.16 and $SUV_{\text{max}}$ was 3.29 in December 2003 (Fig. 2c). In addition, MR imaging showed progressive spinal cord swelling (Fig. 1d). From these findings, open biopsy of the cervical spinal lesion was performed. Histopathological examination of the surgical specimen revealed disseminated medulloblastoma. He received ICE chemotherapy, but MR imaging demonstrated progressive disease. He died of tumor dissemination in June 2005.

**Case 3**

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A 3-year-old boy was admitted to our department presenting with a respiratory disorder in June 2002. T1-weighted MR images with Gd-DTPA demonstrated a heterogeneously enhanced mass lesion in the fourth ventricle and the cisterna magna (Fig. 1e). The lesion was completely removed, and the tumor was histologically diagnosed as choroid plexus carcinoma. Postoperatively, he received irradiation consisting of 24 Gy to the whole brain and spinal cord, and 26 Gy to the posterior fossa. The patient had no sign of recurrence during the three years. MR imaging, however, demonstrated that newly disseminated enhanced lesion in the posterior wall of the third ventricle in August 2005 and in the fourth ventricle and right lateral ventricle in April 2006 (Fig. 1f), respectively. He received ICE chemotherapy from June 2006 to September 2006. MET-PET in March 2007 indicated elevated uptake in the fourth ventricle lesion in which SUV\textsubscript{max} was 1.5 (Fig. 2d). These disseminated lesions gradually expanded the last two years, and he is currently receiving gamma-knife surgery for the recurrent tumors.

**Discussion**

Despite impressive improvements in therapy of medulloblastoma, the median survival time following tumor recurrence is 1.8 years\textsuperscript{3).} The prognosis of choroid plexus carcinoma with metastases is also grave\textsuperscript{4).} Considering the dismal prognosis of the patients with malignant brain tumors associated with metastases, recurrent tumors described in this article exhibited surprisingly static courses. In case 1, disseminated lesions showed almost no changes for six years without any additional treatments. In case 2, spinal intramedullary metastasis at initial diagnosis showed extremely slow progression for four years. However, it suddenly demonstrated rapid progression afterward and resulted in death. In case 3, disseminated lesions emerged three years after the initial treatments, and slowly expanded during the two years. There are few reports that clinically apparent metastases and disseminations can remain static for a long period in pediatric malignant brain tumors.

The role of MET-PET is recently well-established in the estimation of malignancy of glioma and differential diagnosis between radiation induced necrosis and tumor recurrence\textsuperscript{5,6).} The mechanism of accumulation of MET in tissues are thought to present disruption of blood brain barrier, abundant vessels, and active carrier-mediated transport across the cell membrane\textsuperscript{7).} Therefore, its accumulation is thought to increase protein synthesis by neoplastic tissue proliferation, and a significant uptake in MET-PET is considered to reflect the existent of viable tumor cells. Sonoda et al. reported that the ratio
of tumor tissue to contralateral gray matter on MET-PET of recurrent glioma was significantly higher than that of radiation necrosis\(^8\). Tsuyuguchi et al. also reported that MET-PET was useful in differentiating recurrent metastatic brain tumor from radiation necrosis\(^9\). Considering the advantage of MET-PET in visualizing the metabolism of the tumor, we attempted to use MET-PET in the present three cases to elucidate the metabolic activities in the clinically static metastatic lesions.

Although metastatic and disseminated lesions in the present three cases remained stable for a long period, MET-PET studies revealed increased uptake of these lesions. Therefore, they were thought to be metabolically active and still have proliferative potential despite their static behaviors. This fact raises the possibility that metastatases and disseminations in a static course may suddenly show lethal progression. Indeed, the recurrent tumor of the spinal cord in case 2 expanding very slowly for four years showed striking growth and became lethal after MET-PET revealed increased uptake\(^6\). This case indicates that MET-PET may be useful in the prediction of the drastic progression of the clinically static metastases. Careful follow-up of MET-PET is needed even if the recurrent tumor shows a static course.

References

Figure 1. (Case 1) a, Preoperative T1-weighted magnetic resonance (MR) imaging with gadolinium-diethylenetriaminepenta-acetic acid (Gd-DTPA) demonstrating a mass lesion in the cerebellar vermis. b, Follow-up MR imaging, obtained in February 1999, revealing a enhanced recurrent tumor in the cerebellar vermis (arrow). (Case 2) c, Preoperative T1-weighted MR imaging with Gd-DTPA showing a mass lesion in the cerebellar vermis. d, T1-weighted MR imaging with Gd-DTPA of the spine demonstrating spinal cord swelling from C5 to Th1 in July 2003 (arrow). (Case 3) e, Preoperative T1-weighted MR imaging with Gd-DTPA revealing a heterogeneously enhanced mass lesion in the fourth ventricle and the cisterna magna. f, Follow-up MR imaging, obtained in April 2006, showing a enhanced recurrent tumor in the fourth ventricle (arrow).

Figure 2. (Case 1) a, $^{11}$C-methionine-positron emission tomography (MET-PET) in June 2007 indicating that the enhanced lesion in the cerebellar vermis has elevated uptake of $^{11}$C-methionine (arrow). (Case 2) b, c, Serial MET-PET indicating progressive elevated uptake in the spinal cord lesion. (Case 3) d, MET-PET in March 2007 indicating elevated uptake in the fourth ventricle lesion (arrow).