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著者	Misaki Kouichi, Nakada Mitsutoshi, Mohri Masanao, Hayashi Yutaka, Hamada Jun-ichiro
journal or publication title	Brain Tumor Pathology
volume	28
number	3
page range	259-263
year	2011-07-01
URL	http://hdl.handle.net/2297/29468

doi: 10.1007/s10014-011-0033-5

MGMT promoter methylation and temozolomide response in choroid plexus carcinoma

Kouichi Misaki · Mitsutoshi Nakada ·
Masanao Mohri · Yutaka Hayashi ·
Jun-ichiro Hamada

Received: 30 October 2010 / Accepted: 8 March 2011 / Published online: 26 March 2011
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Abstract Choroid plexus carcinoma (CPC) is a malignant tumor with a strong tendency to spread along the cerebrospinal fluid pathway. There is no standardized chemotherapy protocol for this rare tumor. We report a 38-year-old man with CPC in the lateral ventricle with obstructive hydrocephalus. Because of the poor demarcation between thalamus and fornix, subtotal tumor resection was performed. Postoperative spine magnetic resonance (MR) image revealed whole spinal axis dissemination. After diagnosis of CPC, the patient was treated with whole ventricular and spine radiation concomitant with temozolomide chemotherapy, although the *O*₆-methylguanine-DNA methyltransferase (MGMT) promoter was found to be unmethylated. Although MR images revealed transient stable disease during adjuvant therapy, tumor progression was depicted after four cycles of temozolomide therapy. We discuss the ineffectiveness of adjuvant temozolomide therapy for CPC in connection with *O*₆-methylguanine-DNA methyltransferase promoter methylation.

Keywords Choroid plexus carcinoma · Temozolomide · MGMT · Methylation

Introduction

Choroid plexus tumors (CPT) are rare intraventricular papillary neoplasms, comprising 0.4–1.0% of primary

brain neoplasms and predominantly occurring in young children [1–5]. Choroid plexus carcinoma (CPC), which shows histological malignancy, represents between 8% and 25% of all CPTs [2, 3, 6–8]. The outcome of benign choroid plexus papilloma (CPP) is usually excellent following gross total resection, whereas the more aggressive biological behavior of CPC necessitates postoperative adjuvant treatment [1, 9]. Chemotherapy has led to remission of choroid plexus carcinoma but does not always improve survival or avert recurrence [1, 10–12]. The DNA-alkylating agent temozolomide is effective for malignant gliomas, whereas evidence for its efficacy for CPT remains unclear [7, 12–14]. Promoter methylation of the *O*₆-methylguanine-DNA methyltransferase (MGMT) DNA-repair gene is a marker for the response to alkylating agents in malignant gliomas, although this has not been probed in CPT [13–15]. Herein, we report an adult case of CPC with craniospinal seeding who underwent subtotal resection followed by administration of temozolomide with assessment of MGMT promoter methylation status.

Case report

Clinical course

A 38-year-old previously healthy man presented with a 5-month history of intermittent headache and memory impairment. Magnetic resonance (MR) images demonstrated a heterogeneously enhanced mass that showed bilateral extension from the septum pellucidum with obstructive hydrocephalus (Fig. 1a, b). He underwent tumor resection via the interhemispheric transcalsal approach. A small part of the mass was left because it was adhered to the fornix and thalamus (Fig. 1c). Hydrocephalus was treated

K. Misaki (✉) · M. Nakada · M. Mohri · Y. Hayashi ·
J. Hamada

Department of Neurosurgery, Division of Neuroscience,
Graduate School of Medical Science, Kanazawa University,
13-1 Takara-machi, Kanazawa, Ishikawa 920-8641, Japan
e-mail: misaki@ns.m.kanazawa-u.ac.jp

with a ventriculoperitoneal shunt. Radiation therapy was initiated 3 weeks after tumor resection with administration of temozolomide as described later. Three months after tumor removal, spine MR images demonstrated entire spinal axis dissemination with the largest lesion at the level of T3; at that time, the patient suffered from progressive paraparesis (Fig. 1d, e). Chest, abdominal, and pelvic computed tomography excluded systemic malignancy.

Pathological findings

Pathologically, the tumor showed blurring of the papillary pattern, which was composed of atypical epithelial cells with brain invasion (Fig. 2a, b). There was brisk mitotic activity with an MIB-1 staining index of 14.2% (Fig. 2c). Tumor cells were positive for cytokeratin, epithelial membrane antigen (EMA), and carcinoembryonic antigen (CEA) (Fig. 2d), but negative for transthyretin, S-100 protein, glial fibrillary acidic protein (GFAP), and synaptophysin. The tumor was diagnosed as a CPC.

Analysis of MGMT promoter methylation

The methylation-specific polymerase chain reaction (PCR) assay, known as MSP, was performed to evaluate the methylation status of MGMT promoter in the tumor tissue. DNA was extracted from the formalin-fixed, paraffin-embedded tissue sample. After bisulfate modification of the DNA, the MSP assay was performed at least three times. In

the case of our patient, the MGMT promoter was found to be unmethylated (Fig. 3) [13, 14, 16, 17].

Adjuvant therapy

Combined radiation and chemotherapy were performed. The tumor bed, whole ventricular, and whole spine were treated with 60, 30, and 30 Gy, respectively. The patient also received simultaneous adjuvant temozolomide therapy at 75 mg/m²/day (140 mg daily). Four weeks after completion of radiation therapy, the temozolomide dose was increased to 150 mg/m²/day (260 mg daily) for 5 consecutive days per 4 weeks; four cycles were completed without significant toxicity. Although MR images during the adjuvant therapy revealed transient stable disease, multifocal spread of tumor was depicted at the final chemotherapy. The patient died of respiratory failure caused by dissemination around the brainstem 11 months after the initial surgery (see Fig. 1f).

Discussion

Histologically, CPP corresponds to World Health Organization (WHO) grade I, atypical CPP, which is defined as CPP with increased mitotic activity to grade II and CPC to WHO grade III. CPC shows frank signs of malignancy, including nuclear pleomorphism, frequent mitoses, high nucleus-to-cytoplasm ratios, increased cellular density,

Fig. 1 Brain and spine T₁-weighted magnetic resonance (MR) images with gadolinium contrast. **a, b** Axial (**a**) and coronal (**b**) images demonstrated the heterogeneous mass extending bilaterally from the septum pellucidum. The tumor was directly contiguous with the bilateral thalami. **c** Postoperative coronal image showed a small residual tumor between the bilateral thalami (*arrow*). **d, e** Sagittal spine MR images revealed multiple subarachnoid enhanced lesions in the whole spinal axis (*arrows*). **f** Sagittal image of craniocervical junction demonstrated multiple seeding lesions around brainstem and cervical cord (*arrows*)

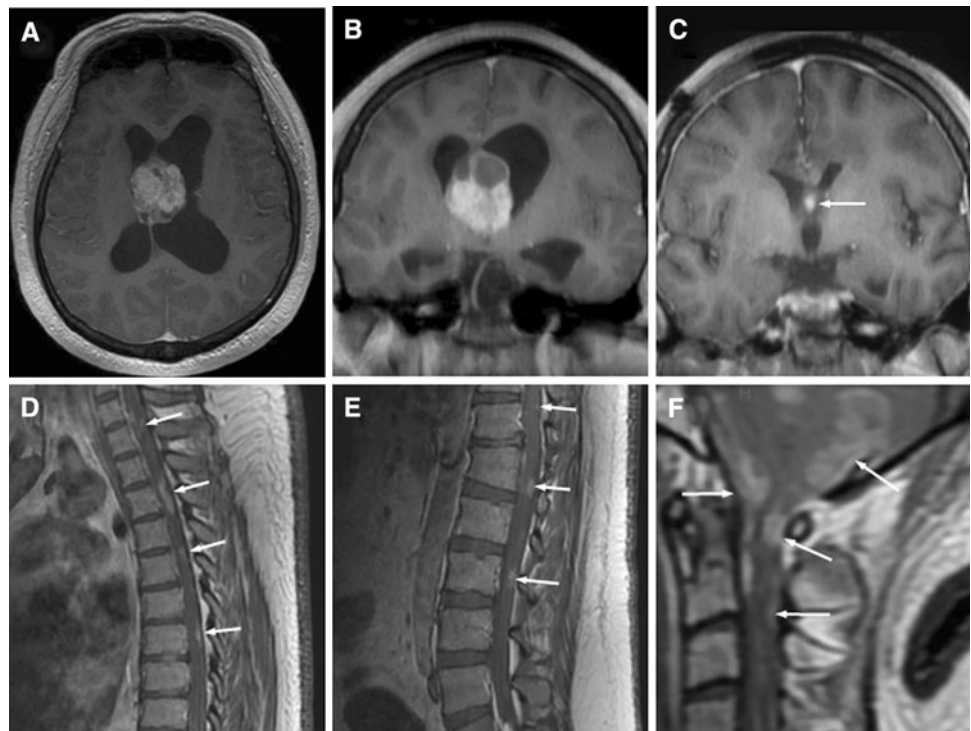


Fig. 2 **a** Hematoxylin and eosin staining showed atypical epithelial cells arranged in papillary-like projections, with abundant mitoses. **b** Tumor showed invasion to adjacent brain. **c** MIB-1 staining index was 14.2%. **d** Partial cytokeratin positivity was demonstrated in the tumor cells. Bars 100 μ m

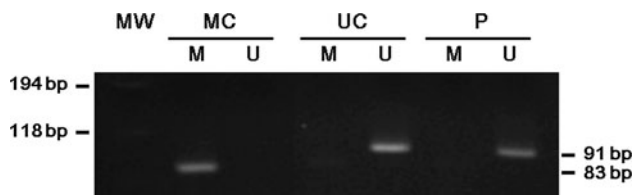
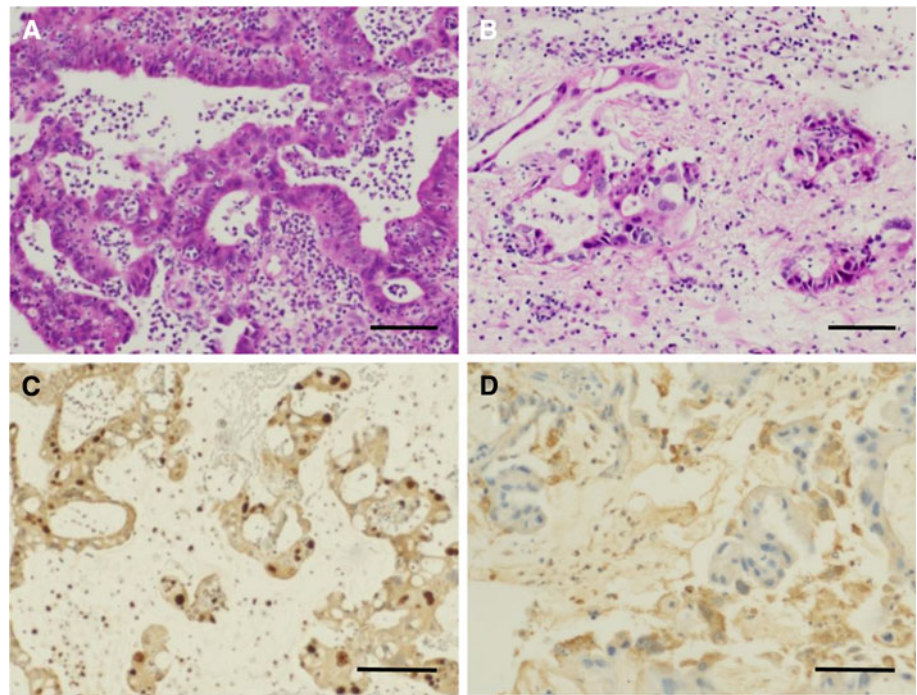


Fig. 3 Polymerase chain reaction (PCR) products in the *M* lanes indicate methylation of *O*₆-methylguanine-DNA methyltransferase (*MGMT*) promoter. *MC*, U87 cell line as methylated control; *UC*, U138MG cell line as unmethylated control; *P*, patient's tumor sample; *MW*, molecular weight marker

blurring of the papillary pattern with poorly structured sheets of tumor cells, necrotic areas, and often diffuse brain invasion [5]. The reported mean MIB-1 staining index is 1.9% for CPP and 13.8% for CPC [5]. Immunohistochemically, cytokeratin and vimentin are frequently expressed in CPP and CPC whereas transthyretin, which is a specific marker for CPT, S-100 protein, and GFAP, is less frequently expressed in CPC than in CPP [5, 18, 19]. Immunodetection of CEA and EMA is variously reported in CPT [5, 19, 20]. The differential diagnosis of CPC includes metastatic adenocarcinomas and anaplastic ependymomas [4, 21, 22]. The present case did not have primary systemic tumor and perivascular pseudorosettes and showed evidence of frequent mitoses, brain invasion, and expression of cytokeratin; these findings were consistent with CPC. Negative staining for transthyretin and S-100 protein such as the present case is reported to correlate with poor prognosis in CPT [19].

In the treatment of CPC, the extent of surgery is a significant prognostic factor [1, 6, 8, 10, 11, 23]. Packer et al. [11] reported relapse in five of six patients who had partial resection for CPC compared to one of five patients with total resection. A meta-analysis revealed that CPC patients had a 2-year survival rate of 72% and 34% for those with gross total resection and those with incomplete resection, respectively [1]. Although aggressive surgical resection of the tumor is essential for long survival, radical resection is restricted by the tendency to invade adjacent brain [18]. The present case could not achieve gross total resection because of tumor adhesion to fornix and thalamus. In cases of incomplete tumor removal or craniospinal metastasis, postoperative adjuvant therapy is strongly recommended.

CPT has a tendency to cause metastases along cerebrospinal fluid pathways [4, 18, 23–28]. A review of CPT showed that the incidence of metastasis is 12–50% in its clinical course [1, 23]. Metastasis is more frequent in CPC and a significant factor affecting the survival time in CPT [1, 23]. Dissemination is also detected postoperatively, as in the present case [7, 18, 27, 28]. Because spine MR imaging was not performed before the initial surgery, it remains unclear whether surgery was responsible for tumor cell seeding, which is described as drop metastasis.

Several reports demonstrated that postoperative irradiation confers a survival advantage in patients who have undergone a subtotal resection as well as gross total resection [1, 9, 10, 24, 29]. Some authors recommend regional radiation [30] whereas others performed craniospinal radiation [11, 24]. Information concerning

Table 1 Summary of temozolomide therapy for choroid plexus tumors

References	Age/sex	Pathology	Site of origin	Dissemination	MGMT promoter	Temozolomide	Follow-up (after dissemination)
McCall [7]	30/F	CPP	Fourth ventricle	Yes	NA	12 cycles	17 months: stable
	22/F	CPP	Fourth ventricle	Yes	NA	18 cycles	4 years: progression
Lozier [12]	68/F	CPC	Temporal lobe	No	NA	6 cycles	44 months: stable
Present case	38/M	CPC	Lateral ventricle	Yes	Unmethylated	4 cycles	11 months: dead

CPC choroid plexus carcinoma, CPP choroid plexus papilloma, MGMT *O*₆-methylguanine-DNA methyltransferase, NA not available

appropriate doses and extent of radiation needed is still lacking [12, 18]. For CPC patients, because dissemination and relapses outside the primary site are likely to occur, craniospinal radiation therapy should be considered, especially in adults who have less risk of intellectual sequelae caused by radiation than do children [11]. In the present case, the patient showed preoperative memory impairment caused by tumor invasion to the fornix. Radiation-induced encephalopathy causes cognitive disturbances such as mental slowing and deficits in attention and memory in adults as well as children [31]. Kleinberg et al. [32] demonstrated that adult patients receiving partial brain irradiation tended to retain better memory functions than those receiving whole brain treatment. Therefore, we selected whole ventricular radiation instead of whole brain radiation to avoid progression of intellectual disorder. Although the overall survival of CPC patients resected partially with craniospinal irradiation was reported to be significantly better than that without irradiation, the 2-year overall survival rate of those with irradiation was only about 50% [1]. This result indicated requirement of adjuvant chemotherapy, particularly for CPC patients with obvious dissemination such as the present case.

There is no standardized chemotherapy protocol for this rare tumor [1, 10–12]. Although meta-analysis of CPC demonstrated that etoposide was the most effective drug, the response rate was only less than half of cases [33]. Several reports demonstrated efficacy of temozolomide for CPTs (Table 1) [7, 12]. In two cases of recurrent CPP with craniospinal dissemination treated with temozolomide, one case showed radiographically stable disease for 17 months after surgery, whereas in the other case tumor control failed [7]. In one case of adult CPC without dissemination treated with temozolomide after gross total resection, no evidence of recurrence was seen for 44 months after surgery [12]. However, these cases received temozolomide chemotherapy without analysis of MGMT promoter methylation. Hasselblatt et al. [15] reported that aberrant methylation of MGMT promoter was confirmed in seven of eight cases in CPC without evaluation of the temozolomide efficacy. Our case may be rare with lack of methylation of the MGMT promoter. As there were no other potent chemotherapeutic

agents and no evidence of MGMT promoter methylation status as to temozolomide efficacy in CPC, we administered temozolomide for the present case. Unfortunately, our case did not receive any benefit from temozolomide, which may suggest that unmethylation of the MGMT promoter predicts the ineffectiveness of temozolomide for CPC as well as glioblastoma. The ineffectiveness of temozolomide might also be lack of a DNA mismatch-repair system that recognizes DNA mismatches caused by temozolomide and repairs resynthesis of DNA. The DNA mismatch-repair system causes repeated futile mismatch-repair cycles, creating DNA strand breaks and cytotoxicity. The lack of this system leads to ineffectiveness of temozolomide [34]. To our best knowledge, this is the first report of a CPC that was treated with temozolomide, coupled with assessment of MGMT promoter methylation. A large population of CPC cases will be needed to confirm this speculation.

Acknowledgments This report is not associated with any financial support or grants.

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