Intraoperative Radiation Therapy and Chemotherapy for Huge Choroid Plexus Carcinoma in an Infant

—Case Report—

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Abstract

A 2-month-old boy presented with a huge choroid plexus carcinoma in the left cerebral hemisphere. Almost total resection of the tumor was achieved, but a remnant abruptly enlarged 5 months later, requiring reoperation. After radical resection of the tumor, intraoperative radiation (10 Gy) was delivered. Postoperative chemotherapy was performed with methotrexate and vincristine, selected on the basis of *in vitro* chemosensitivity testing. No recurrence of the tumor was detected 18 months after the second operation. Radical surgery with these adjuvant therapies may be a good method to control this aggressive disease in infants.

Key words: chemotherapy, chemosensitivity test, choroid plexus carcinoma, intraoperative radiation therapy, magnetic resonance imaging, operation

Introduction

Neoplasms derived from the epithelium of the choroid plexus are rare, forming about 0.4–0.6% of all intracranial tumors.²⁵⁾ They are classified into the benign papilloma type and malignant carcinoma type.^{12,19,25)} Choroid plexus carcinoma is rarer and comprises 10–20% of choroid plexus tumors.^{9,15,17)} The prognosis for this disease is generally poor.^{5,7,10,17)} Radical surgical excision and postoperative irradiation are the best treatments for prolonged survival in patients with choroid plexus carcinoma.⁶⁾ However, radiotherapy in young patients is controversial because neurological impairment may subsequently occur.¹¹⁾ The benefits of adjuvant chemotherapy are still under discussion.¹⁷⁾

We describe a case of large choroid plexus carcinoma managed by radical resection, intraoperative radiation therapy (IORT),^{14,20,21)} and chemotherapy using agents selected by *in vitro* chemosensitivity testing.^{1,3)}

Case Report

A 2-month-old boy was admitted to our hospital because of head enlargement. His head circumference was 33 cm at birth, and reached 48 cm at 2 months old when he became progressively more irritable. On admission, his body weight was 6700 g and his head circumference was 48.5 cm. The left side of his cranium was tender and projected unevenly. The sun-set phenomenon was observed. The hypertonic lower extremities showed sustained clonus at the knees and ankles. Plain craniography showed enlargement of the skull and marked decalcification of the left side of the vertex. Magnetic resonance (MR) imaging showed a large ventricular tumor which was about 9 cm in diameter. The tumor was composed of an intensely enhanced solid portion, signal void foci, and multiple cysts (Fig. 1). Angiography demonstrated a prominent tumor stain fed by the anterior and posterior choroidal arteries, the cortical branches of the middle cerebral artery, and the anterior cerebral artery. Early draining veins were seen within the tumor stain.

He underwent a left frontotemporoparietal craniotomy in August 1993. The atrophic cerebral

Fig. 1 Preoperative MR images with gadolinium enhancement, axial (*left*), sagittal (*center*), and coronal (*right*) views, demonstrating the huge enhanced tumor in the left hemisphere, the presence of high flow large vessels (*arrowheads*), and multiple cyst formations around the tumor (*arrows*).

Fig. 2 Photomicrographs of the first tumor specimen. *upper left*: The neoplastic cells have a uniformly columnar shape and papillary arrangement. HE stain, $\times 200$. *upper right*: The neoplastic cells show solid growth patterns. HE stain, $\times 100$. *lower left*: The cells vary considerably in size, with marked variation in nucleus size, shape, and staining intensity. HE stain, $\times 200$. *lower right*: Many mitoses are present. HE stain, $\times 400$.

cortex overlying the tumor was incised. Initially the tumor blood supply from the choroid plexus could

not be secured. We debulked the tumor internally and separated the surrounding gliosis tissue *via* the

Fig. 3 Axial MR images with gadolinium enhancement, 2 months after the first operation (*upper row*) showing the almost total resection of the huge tumor, with clots in the ventricles and the subdural space, and a small enhanced mass in the parietal region (*arrow*); and before the second radical operation (*lower row*) showing the enhanced mass at the parietal region has enlarged abruptly.

multiple peritumoral cyst formations. These procedures were accompanied by substantial hemorrhage. Finally, the very vascular-rich tumor was totally resected en bloc. He lost as much as 3805 ml of blood, but his intraoperative and postoperative course was uneventful.

Histological examination of the tumor specimen revealed choroid plexus carcinoma. The tumor included normal-appearing choroid plexus, papillomatous proliferation, and carcinomatous lesions (Fig. 2). The tumor cells in the papillomatous areas had a uniform columnar shape and papillary arrangement. The carcinomatous areas contained tubular and solid growth patterns. The nuclei showed mitoses and marked variation in size, shape, and staining intensity. There were extensive areas of necrosis and hemorrhage. Proliferation of vascular structures was also observed.

Postoperative computed tomography revealed total removal of the tumor. A ventricular shunt was implanted 3 weeks after the first operation due to hydrocephalus. Cytological examination showed his cerebrospinal fluid contained no malignant cells. Postoperative MR imaging 2 months after the first operation showed almost total resection of the huge

tumor except for a small enhanced mass in the parietal region (Fig. 3 *upper row*). Hypertonicity of the bilateral lower extremities was diminished. His weight increased to 7200 g after discharge home. He was followed up with monthly MR imaging, which showed abrupt enlargement of the enhanced mass at the parietal region (Fig. 3 *lower row*). He was readmitted to our hospital 5 months after the first operation. At this time, right motor weakness was observed.

A second left frontotemporoparietal craniotomy was performed in February 1994. The tumor was covered with an internal capsule of chronic subdural hematoma. The tumor was dissected from the tentorial surface, the falx, and the frontal lobe, and then totally resected en bloc (Fig. 4 *upper row*). IORT was performed using 10 Gy of beta-irradiation. The irradiation was designed to penetrate 1–1.5 cm deeper than the surface of tumor cavity. The radiation field was 4 cm in diameter and focused on the choroid plexus. The histology of the specimens was the same as those from the first operation.

The surgical specimen was mechanically and enzymatically dissociated under aseptic conditions. The digested tumor tissue was passed through a 70 μ m

Fig. 4 Axial MR images with gadolinium enhancement, 2 weeks after the second operation (*upper row*) showing the total removal of the tumor; and 18 months after the second operation (*lower row*) showing no tumor recurrence.

pore cell strainer and incubated on culture dishes in Dulbecco's minimum essential medium containing 20% fetal calf serum under conventional culture conditions. Cisplatin, etoposide, 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride (ACNU), vincristine, and methotrexate were added to these primary cultures. Growth inhibition was evaluated with a microculture tetrazolium assay.³⁾ Culture plates were tested in duplicate. Vincristine and methotrexate were the most effective growth inhibitors. ACNU and cisplatin achieved minimal growth inhibition even at high concentrations. The concentration achieving 90% growth inhibition (IC_{90})¹⁾ was 0.9 ng/ml for vincristine and 38 ng/ml for methotrexate.

Based on the chemosensitivity testing, 0.5 mg of vincristine and 2 mg of methotrexate were administered intravenously per day. The expected serum concentration to be obtained by intravenous injection was higher than the IC_{90} shown by *in vitro* chemosensitivity testing.^{16,26)} The blood-brain barrier is absent at the choroid plexus, so these agents should easily penetrate into the tumor tissue. This protocol was performed once a week, for a total of four times.

He was discharged 2 months after the second operation. His right motor weakness, observed before the

second admission, gradually improved. His body weight increased to 9500 g. He received maintenance therapy of intravenous administration of 0.5 mg of vincristine and 2 mg of methotrexate once a month. MR imaging 18 months after the second radical operation showed no recurrence of the tumor (Fig. 4 *lower row*). His development was evaluated as that of a 7-month-old boy.

Discussion

There are several histological criteria for the diagnosis of choroid plexus carcinoma. Many authors^{12,19,24)} suggest tumor invasion into brain tissue as a diagnostic criterion. However, tumor invasion is difficult to demonstrate if the surgical specimen does not contain surrounding brain tissue. Ellenbogen *et al.*⁹⁾ suggest the following are essential for the diagnosis of choroid plexus carcinoma: areas with loss of differentiated papillary architecture, and malignant cellular features such as mitoses and nuclear pleomorphism. Our case fulfilled all these criteria.

The biological behavior of choroid plexus carcinoma is poorly characterized.¹⁷⁾ The histological appearance of choroid plexus carcinoma does not necessarily indicate the biological behavior, as many highly anaplastic choroid plexus neoplasms are clinically be-

nign.⁴⁾ However, the survival period for patients with choroid plexus carcinoma is generally poor.^{5,7,17)} The time from onset of symptoms to death was approximately 9 months in children and 3.5 years in adults.⁷⁾ More recently, Ellenbogen *et al.*⁹⁾ reported a 5-year survival rate of 50% in 14 children with choroid plexus carcinoma.

Surgery may have a critical impact on the progression-free survival of the patient with choroid plexus carcinoma. Operative morbidity and mortality of choroid plexus tumors in children are associated mainly with excessive blood loss.⁹⁾ Our patient had an uneventful intraoperative and postoperative course despite the loss of as much as 3805 ml of blood, which was due to modern neuroanesthetic techniques. Surgical success with this disease absolutely requires the constant attention of well-trained pediatric anesthesiologists.²³⁾ In addition, the presence of the peritumoral cyst formations^{13,22)} contributed to the successful dissection and resection of this very vascular-rich tumor.

Radiation therapy is also necessary at least at recurrence.^{15,17)} In fact, most children with choroid plexus carcinomas achieving long-term survival had received radiation therapy.¹⁰⁾ However, extensive radiation of the young causes severe intellectual and endocrinological sequelae.¹¹⁾ In our patient, we found that surgical resection alone was not enough to control this aggressive tumor because of the very rapid growth of the recurrent tumor. Therefore, IORT and chemotherapy with agents selected by chemosensitivity test were used to control the tumor and minimize neurological damage. The efficacy of IORT remains to be established. IORT is reported to be significantly effective in the "induction of remission" following surgical excision of malignant gliomas.^{14,20,21)} IORT minimizes damage to normal tissue through the direct visualization of the tumors during surgical exploration. This advantage is particularly beneficial to young patients. The development of our patient was delayed significantly. However, this may have been the result of primary brain damage by tumor growth rather than radiation therapy.

Only a few cases of choroid plexus carcinoma have been treated successfully by chemotherapy alone or in combination with radiation therapy.^{1,2,8,10)} Eight-drugs-in-one-day treatment¹⁸⁾ was reported effective with this disease.¹⁰⁾ However, the toxicity of chemotherapy cannot be ignored.¹⁸⁾ Effective agents against the tumor *in vitro* are not always effective *in vivo*, but agents ineffective *in vitro* must be ineffective *in vivo*. Chemosensitivity testing showed administration of ACNU or cisplatin would be ineffective in our patient because these agents did not in-

hibit the tumor growth *in vitro*. Such *in vitro* testing may be useful to obtain optimal effect and minimal toxicity by chemotherapy.

The optimum treatment for choroid plexus carcinomas is still unclear. We think a better prognosis for choroid plexus carcinoma can be obtained by total resection of the tumor with suitable adjuvant therapy, such as IORT and chemotherapy using agents confirmed to be effective against the tumor *in vitro*. Further intensive follow-up study is necessary for this infant.

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