Management of Pilomyxoid Astrocytomas: Our Experience

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Abstract. *Background: Pilomyxoid astrocytoma (PMA) shows a higher rate of recurrence and cerebrospinal fluid (CSF) dissemination than does pilocytic astrocytoma (PA). In this article, we discuss the treatment of PMA. Materials and Methods: Between 1992 and 2007, the authors treated 5 patients. Two of these were male, three female. Their ages ranged from 3 months to 11 years. Results: Three patients showed CSF dissemination on the initial radiographic examination. All patients received chemotherapy; the most commonly used combination drugs were cisplatin (CDDP)/carboplatin (CBDCA) and etoposide. When these drugs were unsuccessful, they were changed or other drugs added to the combination. After chemotherapy, four patients showed remarkable tumor regression. Nevertheless, one patient died 22 months after initial diagnosis, due to tumor progression. Conclusion: While our series was limited to a small number of patients, we have a positive impression of the value of chemotherapy. Even if initial chemotherapy is ineffective, we recommend continued CDDP/CBDCA-based chemotherapy with new drug combinations.*

In 1999 Tihan and his colleague proposed a subtype of pilocytic astrocytoma (PA), which showed histologically and clinically different features from PA (1). These include a monomorphous pattern with a myxoid background, absence of Rosenthal fibers and eosinophilic granular bodies, and more aggressive clinical behavior. The 2000 World Health Organization (WHO) classification of tumors of the central nervous system refer to Tihan's variant as pilomyxoid astrocytoma (PMA) (2). PMAs had the following clinical characteristics: many patients were infants or young children, there was a higher rate of tumor recurrence and cerebrospinal fluid (CSF) dissemination than with PAs, and there was a less favorable prognosis than with PAs. After Tihan's report (1) and those of the 2000 WHO (2), there was an increase in PMA studies (3-17). There were, however, few reports regarding PMA treatment (4, 11, 12, 14). Our intent is to detail our patients' treatments and clinical courses and contribute to the management of PMA.

After Tihan *et al.'s* report in 1999 (1), we treated 3 patients with an initial diagnosis of PMA. In addition, two of the cases diagnosed with PA before 1999 were subsequently classified as a combination of PMA and PA. We reviewed these 5 patients: 2 male and 3 female, ranging in age from 3 months old to 11 years. The follow-up period exceeded 1 year. We evaluated the radiological and pathological findings and our treatments on an individual basis.

Table I and II show the clinical characteristics and the histological features of each case. Three pure PMA patients showed CSF dissemination on the initial radiographic examination. The MIB-1 labeling index (LI) ranged from 4.3% to 16.3% (mean 9.2%). We performed chemotherapy on five patients. Four showed remarkable tumor regression. Nevertheless, the chemotherapy was ineffective for one patient (a 3-month-old boy) who died of tumor progression 22 months after initial diagnosis. With the exception of this case, all patients showed a Karnofsky Performance Score of over 80% during the 22 to 181 month follow-up period.

Case 1

A 3-month-old boy presented remarkable emaciation, weighing 3,434 g (–4.4 S.D.), and had a head circumference of 39.2 cm (–0.9 S.D.). The patient showed diencepharic syndrome. Brain magnetic resonance imaging (MRI) revealed a heterogeneously enhancing large hypothalamic-chiasmatic mass accompanied by obstructive hydrocephalus and CSF disseminations (Figure 1C-E). This tumor was at low intensity on the T1-weighted image (Figure 1A) and at bright intensity on the T2-weighted image (Figure 1B). A ventriculo-peritoneal shunt and tumor

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Key Words: Pilomyxoid astrocytoma, pilocytic astrocytoma, chemotherapy, leptomeningeal dissemination.

Table I. *Clinical characteristics and clinical course of 5 patients.*

Case no.	Gender, age at initial diagnosis	Initial symptoms	Treatment (course of chemotherapy)	Response to treatment	Outcome (months)
1	M, 3 months	Emaciation, hydrocephalus, CSF dissemination	Biopsy 1st: CBDCA, VP-16 (2) 2nd: MCNU, VCR (4) 3rd: CPM, CDDP (1)	 Progression Progression Progression	Death (22 months)
2	M, 7 months	Emaciation, CSF dissemination	Partial resection 1st: CBDCA, VP-16 (2) 2nd: CBDCA, VP-16, IFM (1) 3rd: VCR, CPA, VP-16, CDDP (5) 4th: VCR, CPA, VP-16 (6)	 No change No change Partial remission Complete remission	Alive (36 months)
3	F, 7 years	Headache, hydrocephalus, CSF dissemination	Biopsy 1st: IFM, VP-16, CDDP (3) 2nd: VCR, MCNU, CDDP (6)	 No change Complete remission	Alive (46 months)
4	F, 2 years	Vomiting, hydrocephalus	30 Gy RT	Partial remission	Alive (185 months)
	4 years	Recurrence	Subtotal resection, CDDP, VP-16 (4)	Partial remission	
	11 years	Recurrence	Subtotal resection	Stable	
5	F, 7 years	Gait disturbance, hydrocephalus	Subtotal resection		Alive (131 months)
	10 years	Recurrence	Subtotal resection, 55 Gy RT	Partial remission	
	11 years	Recurrence	CBDCA, VP-16 (12)	Partial remission	
	12 years	Recurrence	γ-kife (marginal dose 14 Gy)	Partial remission	

CSF, Cerebrospinal fluid; CBDCA, carboplatin; VP-16, etoposide; MCNU, ranimustine; VCR, vincristine; CPM, cyclophosphamide; CDDP, cisplatin; IFM, ifosfamide; RT, radiation therapy; mos, months; yrs, years.

Table II. *Pathological features of 5 patients.*

Case no.	Biphasic pattern	Rosenthal fibers	Eosinophilic granular bodyies	Angiocentric arrangement	Vascular proliferation	MIB-1 LI (%)
1	–	–	–	+	+	11.5
2	–	–	–	+	–	8.2
3	–	–	–	+	–	16.3
4	PMA	–	–	+	–	4.3
	PA	+	–	–	–	2.3
5	PMA	–	–	–	–	5.6
	PA	–	–	–	–	Not performed

MIB-1 LI, MIB-1 labeling index; PMA, pilomyxoid astrocytoma; PA, pilocytic astrocytoma.

biopsy were performed. Histologically, the tumor showed proliferation of piloid cells with myxoid backgrounds, monomorphous architecture and angiocentric arrangements (Figure 1F). Our diagnosis was PMA. Chemotherapy using carboplatin 135 mg/m^2 on day one, and etoposide 45 mg/m^2 on days one, two and three was given. Tumor progression was still evident after two courses. The chemotherapeutic regimen was changed to MCNU 70 mg/m^2 on day one and vincristine 1.4 mg/m^2 on day ones and eight. After four courses, the tumor progression continued. The third treatment (one cycle only) was cyclophosphamide 600 mg/m^2 on day one and cisplatin 20 mg/m^2 on day one, two, and three. The chemotherapy was ineffective and the patient died 22 months after the initial diagnosis.

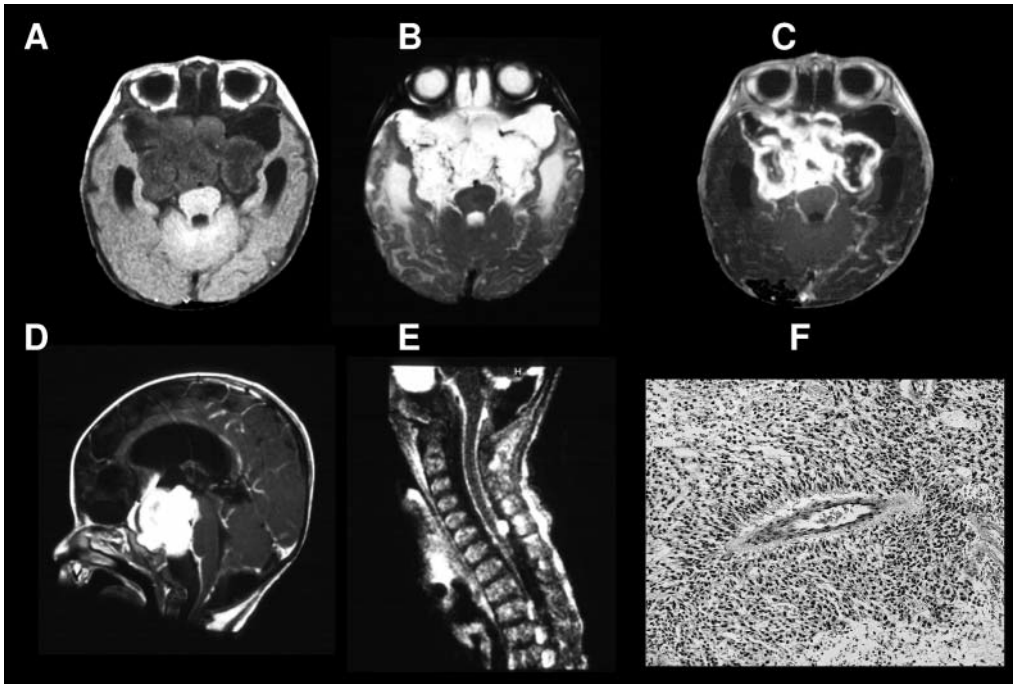

Figure 1. *Case 1. Brain MR images at patient's first presentation. The huge chiasmatic-hypothalamic tumor reveals low signal intensity on a T1-weighted image (A) and bright signal intensity on a T2-weighted image (B). Gadolinium-enhanced brain MR images show heterogeneously strong enhancement (C and D) and leptomeningeal disseminations at the cervical spine levels (E). Surgical specimens show the proliferation of piloid cells accompanied by an angiocentric arrangement (F, H & E: original magnification ×100).*

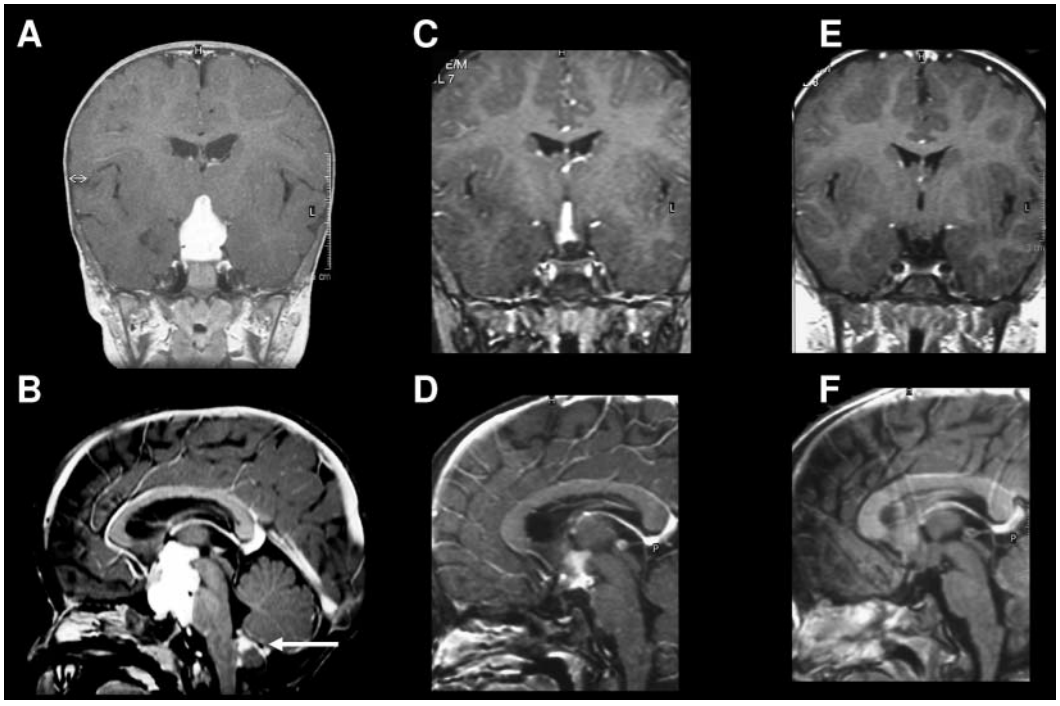

Figure 2. *Case 2. Pre-operative gadolinium-enhanced coronal (A) and sagittal (B) brain MR images showing a chiasmatic-hypothalamic solid mass with homogeneous enhancement and CSF disseminations around the cerebellum (arrow). Gadolinium-enhanced brain MR images (C and D) show tumor size remarkably reduced after five courses of a second chemotherapeutic treatment (cisplatin, etoposide, vincristine, cyclophosphamide). After eleven courses, the patient achieved complete remission (E and F).*

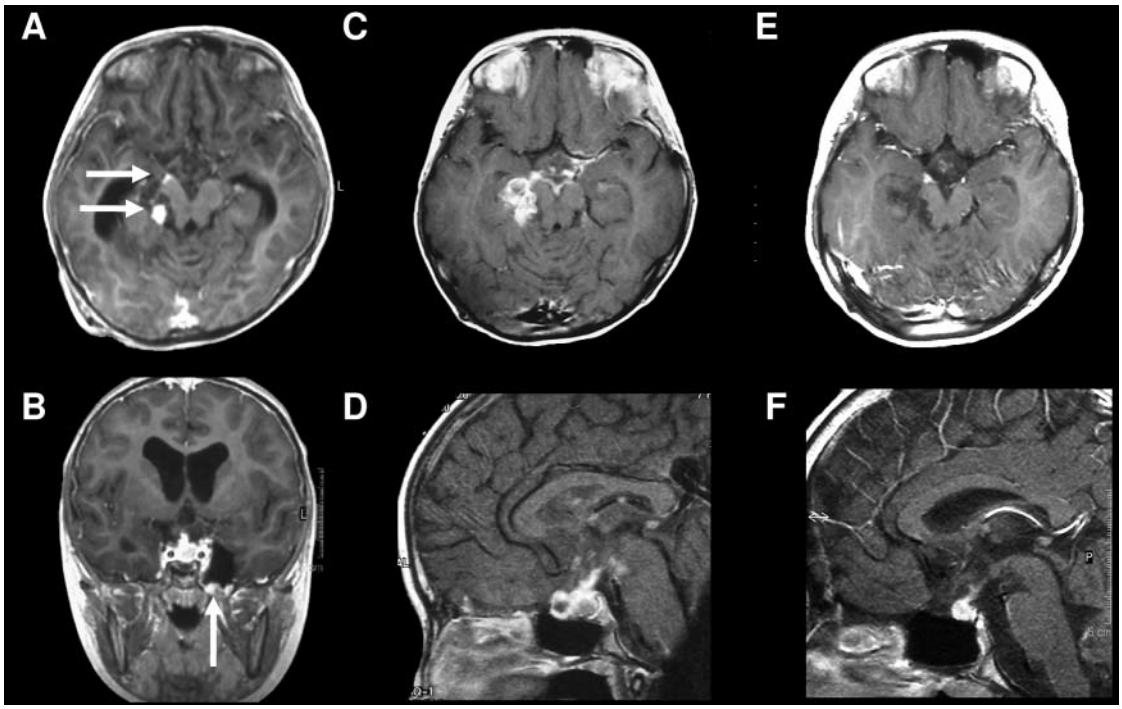

Figure 3. *Case 3. Gadolinium-enhanced brain MR images (A and B) show small enhanced lesions in the suprasellar region, an ambient cistern (arrow), and a left arachnoid cyst (arrow). Gadolinium-enhanced axial (C) and sagittal (D) brain MR images after three courses of the first treatment (cisplatin, ifosfamide, etoposide) show enlargement of enhanced lesions. Gadolinium-enhanced axial (E) and sagittal (F) brain MR images after six courses of the second treatment (cisplatin, vincristine, ranimustine) show remarkably reduced tumor enhancements.*

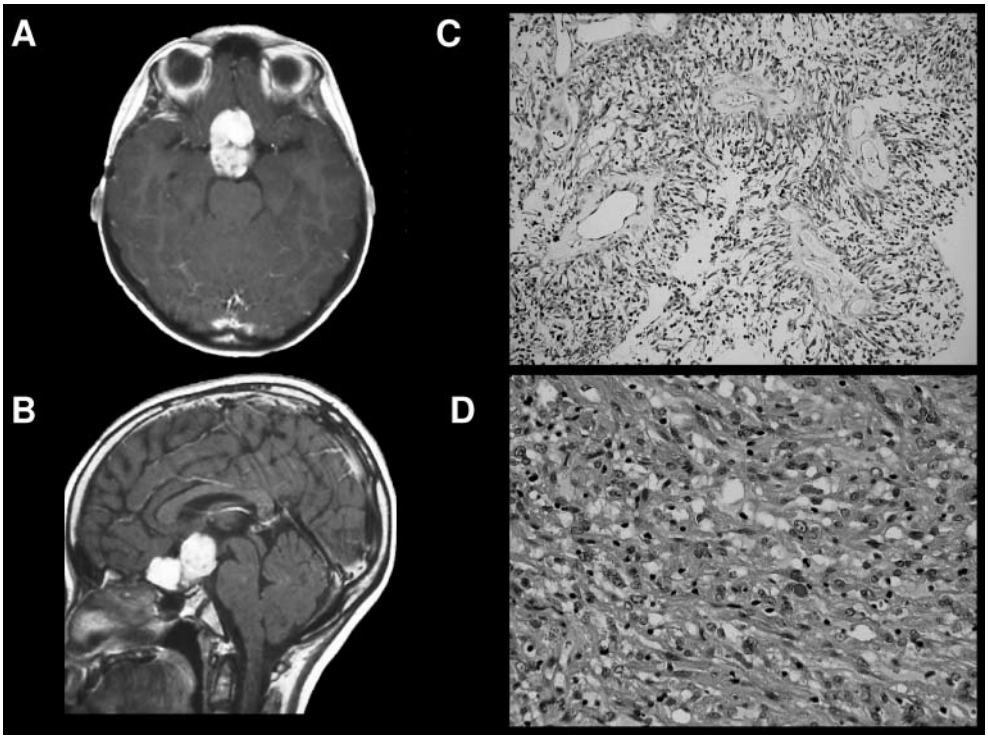

Figure 4. *Case 4. Gadolinium-enhanced axial (A) and sagittal (B) brain MR images on the tumor recurrence show a chiasmatic-hypothalamic enhanced solid mass. Surgical specimens show two different histological features: PMA features composed of angiocentric arrangements (C) and PA features composed of a proliferation of piloid cells accompanied by Rosenthal fibers (D).*

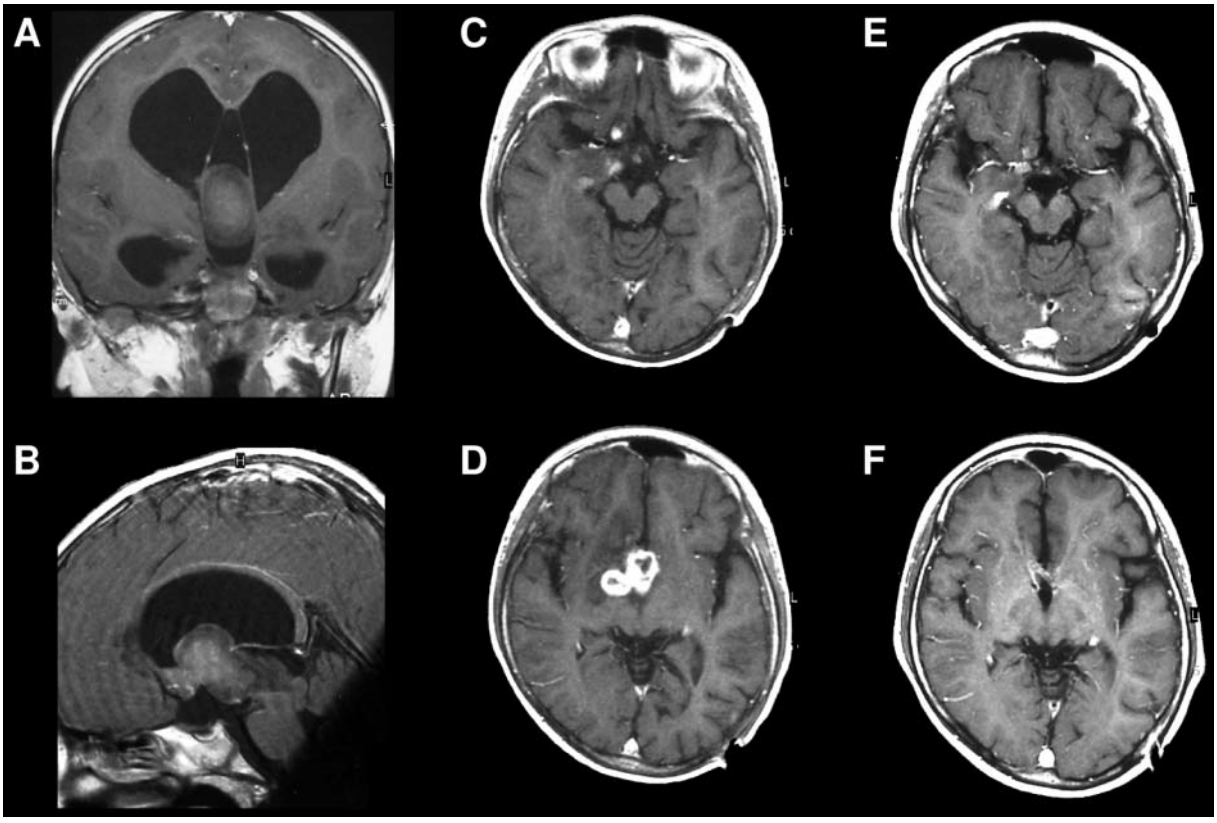

Figure 5. *Case 5. Gadolinium-enhanced coronal (A) and sagittal (B) brain MR images show a slightly enhanced solid mass within the third ventricle. It was accompanied by obstructive hydrocephalus. Four years after the second surgery, gadolinium-enhanced brain MR images show a recurrence of the tumor (C and D). Gadolinium-enhanced brain MR images after twelve courses of chemotherapeutic treatment show remarkably reduced tumor enhancements (E and F).*

Case 2

A 7-month-old boy presented remarkable emaciation, weighing 5,300 g (–3.8 S.D.). The patient showed diencepharic syndrome without neurological deficits. Brain MRI disclosed a homogeneously enhancing large hypothalamic-chiasmatic mass accompanied by CSF disseminations (Figure 2A, B). This tumor revealed slightly low intensity on the T1-weighted image and bright intensity on the T2-weighted image. A tumor biopsy was performed and we made the diagnosis of PMA. Chemotherapy with carboplatin 450 mg/m^2 on day one and etoposide 100 mg/m^2 on days one, two and three was given. After three courses, this combination chemotherapy was ineffective and was changed to vincristine 1.5 mg/m^2 and cyclophosphamide 1,200 mg/m^2 on day one, and etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 on days one through five. After five courses, the use of cisplatin was halted because of hearing loss (Figure 2C, D). After eleven courses of the second combination of regimens, the tumor and the disseminated lesions completely disappeared (Figure 2E, F).

Case 3

A 7-year-old girl complained of headache and nausea. Her brain MRI revealed a homogeneously enhancing sellar mass accompanied by CSF disseminations (Figure 3A, B). A tumor biopsy was performed and we made a diagnosis of PMA. She received chemotherapy with cisplatin 20 mg/m^2, etoposide 60 mg/m^2 and ifosomide 900 mg/m^2 for five consecutive days. After three courses, the regimens was ineffective (Figure 3C, D) and was changed to cisplatin 70 mg/m^2 and MCNU 60 mg/m^2 on day one, and vincristine 1.5 mg/m^2 on days one and eight. After six courses, the size of the tumor and its CSF disseminated lesions underwent extreme shrinkage (Figure 3E, F) and were further stable for two years.

Case 4

An 11-year-old girl was sent to our hospital because of tumor recurrence. At two years of age, she had first presented vomiting. Her head CT revealed hydrocephalus and a suprasellar tumor. The imaging was consistent with

optico-chiasmal low-grade glioma. A surgical biopsy was not performed; instead she received a ventriculo-peritoneal shunt and then local radiotherapy (30 Gy). At 4 years of age, the tumor recurred and was partially removed. After surgery, she had four courses of combinational chemotherapy (cisplatin and etoposide).

Her brain MRI on admission at age 11 revealed a homogeneously enhanced mass in the suprasellar region (Figure 4A, B). Subtotal removal of the tumor was performed. Histologically, the tumor showed two different appearances: angiocentric architecture (PMA, Figure 4C) and solid component accompanied with Rosenthal fibers (PA, Figure 4D). After surgery, no adjuvant therapy was administered. Five years after surgery, the tumor is still progressing very slowly and we are carefully monitoring its growth.

Case 5

A 7-year-old girl complained of gait disturbance. Her brain MRI revealed a slightly enhanced mass within the third ventricle accompanied by obstructive hydrocephalus (Figure 5A, B).

A subtotal removal of the tumor was carried out. The surgical specimen showed biphasic histological features. The loose-textured portions showed the proliferation of bipolar cells in a myxoid background without any Rosenthal fibers or eosinophilic granular bodies. Our diagnosis was a combination of PMA and PA. When she was 10 years old, her tumor recurred. A subtotal removal of the tumor was performed and postoperative radiotherapy (55 Gy) given. Four years later, after a second surgery, the tumor recurred again (Figure 5C, D). Chemotherapy using carboplatin 450 mg/m^2 on the first day and etoposide 100 mg/m^2 on the first day and the next four days was administered. After 12 courses, the tumor shrank remarkably (Figure 5E, F). Two years later at 16 years of age, her health was excellent.

Discussion

In 1999, Tihan *et al*. reported pediatric astrocytoma with monomorphous pilomyxoid features (1). They proposed a subtype of PA, which showed features that were histologically and clinically different from PA. These include a monomorphous pattern with a myxoid background; an absence of Rosenthal fibers and eosinophilic granular bodies; and more aggressive clinical behavior. Before their report, in 1996 Cottingham *et al*. had already pointed out that the classical histological pattern of PA was frequently lacking in infants (18). However, Cottingham *et al*. did not report clinical differences between classic PA and infant PA (18).

The 2000 World Health Organization (WHO) classification of tumors of the central nervous system (2) refers to Tihan *et al*.'s (1) and Cottingham *et al*.'s (18) variant as pilocytic astrocytoma in infants. The 2007 WHO classification describes the variant classified as PMA as a subtype of PA which corresponds to grade II (19). The 2007 WHO classification mentions that PMAs histologically reveal angiocentric cell arrangement and that they exhibite more aggressive biological behavior than typical PAs; in addition, PMAs often show CSF dissemination and local tumor recurrences (19).

After 1999, there was an increase in PMA studies (3-17). Some reports pointed out a close relationship between PMA and PA: Ceppa *et al*. (4), Chikai *et al*. (5), Komakula *et al*. (11), and Fernandez *et al*. (20) noted a maturation or transformation to PA from PMA, and Gotteried *et al*. (10) and Komotar *et al*. (15) discussed PMA and PA hybrid histological features. In our fourth case, we considered histologically hybrid forms, since surgical specimens showed histological features of both PMA and PA. In this case, the compact portions of the tumor showed PA features accompanied by many Rosenthal fibers; on the other hand, the loose-textured portions with myxoid backgrounds showed PMA features accompanied by angiocentric architecture. In addition, there were no eosinophilic granular bodies or Rosenthal fibers in the loose portions. MIB-1 LI was 2.3% in the PA portions and 4.3% in the PMA portions. In case 5, we also considered hybrid forms since surgical specimens showed both PMA and PA histological features. In this case, surgical specimens showed biphasic histological features, but no eosinophilic granular bodies or Rosenthal fibers. MIB-1 LI was 5.6% , which is higher than in classic PA.

PMAs have higher recurrence rates and a poorer prognosis than classic PAs (12-14, 20) and often display CSF dissemination (7, 8, 13, 21). Komotor *et al*. reported that 16 PMA patients (76%) experienced local recurrence and three patients (14.3%) demonstrated CSF dissemination (13). On the other hand, 21 PA patients (50%) experienced local recurrence and there were no patients with CSF dissemination. In their study, 7 PMA patients (33%) and 7 PA patients (17%) died as a result of their disease. Chemotherapy was performed in ten patients (47%), radiotherapy in one patient (5%), and both chemotherapy and radiotherapy in four patients (19%). Unfortunately, Komotor *et al*. did not detail the chemotherapy and radiotherapy used(13).

There are a few limited reports regarding therapeutic strategies for PMA patients (4, 11, 12, 14). Ceppa *et al*.'s initial chemotherapy was preceded by carboplatin and vincristine (4). After twelve courses, the tumor volume was significantly reduced. It recurred several times, however, forcing a change in regimen: vinblastine, temozolomide, etoposide, and cisplatin were administered. Finally, the tumor shrank and remained stable with no evidence of progression in the six years that followed the initial diagnosis. Previous to 1999, as Tihan *et al*. (1), several authors had described the management of aggressive PAs,

especially infantile PAs complicated by CSF dissemination (22-27). These reports can be used to assist in the management of PMA patients. Mamelak *et al*. recommends that patients under 3 years of age be treated with multiagent chemotherapy, but offer no suggestions for chemotherapeutic regimens (24). Petronio *et al*. suggest that nitrosourea-based cytotoxic regimens are useful for the initial treatment of infant and childhood chiasmal/hypothalamic PAs (25). McCowage *et al*. report the successful treatment of CSF dissemination of childhood PAs with high-dose cyclophosphamide (26). Kageji *et al*. also report a successful case with high-dose chemotherapy using a combination of cyclophosphamide, carboplatin and ranimustine (27).

In our first case, chemotherapy was ineffective and the patient died. We started chemotherapy with 30% of the ordinary treatment dose and in its second course administered 50% of the ordinary dose. During this period, the tumor rapidly progressed. Because the effectiveness of cisplatin and carboplatin in tumor suppression depends upon dosage, we conclude that they were not administered in sufficient quantity. With the exception of this instance (case 1), one patient (case 4) achieved disease stabilization and three patients (cases 2, 3, and 5) experienced significant reductions in tumor volume after the chemotherapy. In particular, cases 2 and 3 presented CSF dissemination at the initial diagnosis and responded remarkably well to chemotherapy. The cases showing good response (cases 2, 3, 4 and 5) employing cisplatin/carboplatin-based multiagent chemotherapy. These preliminary results suggest that cisplatin/carboplatin-based multiagent chemotherapy is useful for the initial treatment of PMAs.

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