Int J Clin Exp Pathol 2017;10(11):10700-10710
www.ijcep.com /ISSN:1936-2625/IJCEP0058318

Review Article

Primary intracranial embryonal carcinoma in children: report of two cases with review of the literature

Tao Jiang[1,2], Raynald[1,2], Hongchao Yang[4], Junmei Wang[2], Jiang Du[2], Wenhui Zhang[5], Qiang Shao[3*], Chunde Li[1*]

[1]Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; [2]Beijing Neurosurgical Institute, Capital Medical University, Beijing, China; [3]Department of Neurosurgery, Wuhan Brain Hospital, General Hospital of The Yangtze River Shipping, Wuhan, China; [4]Department of Neurointervention Surgery, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China; [5]Department of Neurology, The 7th Hospital of Baoding, 071000, Hebei, China. [*]Equal contributors.

Received May 26, 2017; Accepted July 14, 2017; Epub November 1, 2017; Published November 15, 2017

Abstract: Embryonal carcinoma is a rare malignant brain tumor and stands for 5% of all intracranial germ cell tumors. Embryonal carcinoma occurs mainly in the posterior third ventricle and pineal region area. Preoperative imaging examination, blood serum and cerebrospinal fluid level of AFP and HCG can support the diagnosis. Subtotal to total removal with good preservation of the important structures can be achieved in this tumor resection. Embryonal carcinoma has poor prognosis result. Postoperative radiotherapy and adjuvant chemotherapy may increase the survival rate, but due to the malignant characteristics of the tumor the 5 years survival rate remains low. We presented two cases of embryonal carcinoma in children. Subtotal resection was achieved in these two patients; patient who had had postoperative radiotherapy and adjuvant chemotherapy had longer survival time than patient who had had surgery alone.

Keywords: Embryonal carcinoma, children, germ cell tumor

Introduction

Germ cell tumors are broadly divided into two classes: germinomatous germ cell tumor (GGCT) and nongerminomatous germ cell tumors (NGGCT). Germ cell tumor constitutes less than 0.5% of all intracranial neoplasms; the incidence varies considerably as according to the geographical area. In western countries, they account for only 0.3-3% of primary central nervous system neoplasms, as opposed to 4-12% of incidence in Japan [1]. Primary intracranial embryonal carcinoma is a rare brain tumor. Embryonal carcinoma is part of the NGGCT classification and stands for about 5% of all intracranial germ cell tumors. Eighty percent of this tumor tends to occur along the midline, such as pineal, suprasellar region, hypothalamus and third ventricle [1-3]. Embryonal carcinoma may also occur in different areas other than the midline, such as basal ganglia, parietal lobe and cerebellum [4-6]. Another unusual location of this tumor, which was in the anterior third ventricle, has reported later by Nsir et al [7]. Embryonal carcinoma usually occurs in adolescence and young adult population (10 to 30 years) [1, 8-11].

The symptoms and signs of embryonal carcinoma are varied depending on the location. In sellar area, visual disturbance is commonly present and some may have diabetes insipidus. Among patients who are older than 12 years old, some may manifest in primary or secondary amenorrhea. Whereas for those patients who are younger than 15 years old, growth retardation may occur; these phenomena may resulted by hypothalamic-pituitary failure. Hydrocephalus and midbrain compression syndrome, such as Parinaud's sign, Argyll Robertson pupil, and diplopia may occur in posterior third ventricle or pineal area embryonal carcinoma. Intracranial hypertension, hemiparesis and epilepsy may occur in the rare case of basal ganglia embryonic carcinoma.

Table 1. Retrospective study of 15 patients with pure embryonal carcinoma

No	Author	Year	Age (years)	Sex	Location	Symptoms	Treatment	Outcome
1	Suwarindr K	1974	5	Male	Cerebellum	Increasing headache and vomiting	Surgery and radiation	Alive 1 year after operation, no tumor recurrence
2	Sakata K	1975	8	Male	Pineal	N/A	Total resection, Bleomycin	Died 4 months after operation dueto tumor metastasis
3	Arita N	1978	8	Male	Pineal	N/A	Surgery, radiotherapy, chemotherapy	Died 11 months after operation
4	Marshal LF	1979	N/A	N/A	N/A	N/A	Surgery, radiotherapy, chemotherapy	Alive 9 months after operation
5	Nakajima F	1981	14	Male	Anterior third ventricle	Vomiting, disturbance of consciousness	Total resection, chemotherapy (cisplatin, vinblastine, bleomycin)	Alive 12 weeks after operation, no tumor recurrence
6	Roger J packer	1984	10	Female	Pineal	Headache, weight loss, decreased vision	Biopsy, radiotherapy	Alive 11 months after operation but had local recurrence, later treated with Cyclophosphamide, Adriamycin, Actinomycin but the treatment had no response, died 4 months later due to diffuse dissemination
			11.5	Male	Pineal	Diplopia, Parinaud's abducens paresis, hydrocephalus	Radiotherapy, chemotherapy (Vincristine, Actinomycin D, Cyclophosphamide)	Alive 6 months after operation, but had local recurrence with ventricular dissemination, later Iridium implants were given but no treatment response, died 2 months later
7	Maeda Y	1990	17	Male	Basal ganglia	Headache, vomiting, right hemiparesis	Total resection, chemotherapy (cisplatin, vinblastine, bleomycin)	Alive 3 months after operation, no tumor recurrence
8	Robin F Koeleveld	1991	7	Male	Right parietal	Focal motor seizure involving the left arm	Total resection, chemotherapy (cyclophosphamide, etoposide), radiotherapy	Alive 21 months after operation, no tumor recurrence
9	Sasaoka Y	1994	15	Male	Basal ganglia	Occasional headache and vomiting, left hemiparesis	Total resection, chemotherapy (etoposide, cisplatin) X 3	Alive 3 months after operation, no tumor recurrence
10	Wang JN	1995	12	Female	Suprasellar	Secondary amenorrhea, decreased visual acuity, dizziness, postprandial vomiting	Subtotal resection	Died 3 weeks after operation
11	Ushio Y	1999	8	Female	Suprasellar	N/A	Biopsy, radiotherapy, cisplatin, etoposide, maintenance therapy cisplatin, etoposide (3X)	Alive 118 months after operation
12	Atef Ben Nsir	2014	15	Male	Anterior third ventricle	High intracranial pressure, generalized tonic-clonic seizure	Total resection, chemotherapy (ifosfamide, etoposide, cisplatin)	Alive 2 years after operation, no tumor recurrence
13	Our case		5	Female	Posterior third ventricle	Paroxysmal headache, nausea and vomiting	Subtotal resection, radiotherapy, chemotherapy (Teniposide, Cisplatin, Ifosfamide)	Alive 6 months after operation, no recurrence of tumor, died 6 months later due to lung metastases
	Our case		2	Female	Pineal	Head tilted to the left and exotropia on the left eye, headache and vomiting	Subtotal resection	Local tumor recurrence 3 months after operation, died 3 months later

Abbreviations: N/A = Not available.

Table 2. Collective studies from other literatures

Author	Year	No. of cases	Outcome	Tumor Histology
Jennings MT	1985	14 cases	2.5 years survival rate (29%)	EC
Matsutani	1997	11 cases	1 year survival rate (45.5%); 3 years survival rate (27.3%); 5 years survival rate (27.3%)	Pure type EC, EST, CC
Sano K	1999	3 cases	1 year survival rate (80%); 3 years survival rate (40%); 5 years survival rate (20%)	EC
Robertson	1997	18 cases	4 year progression free survival (67%)	NGGCT
Calaminus G	1997	19 cases	12 months progression free survival (81%)	NGGCT
Ushio	1997	2 cases	4 year progression free survival (60%)	NGGCT

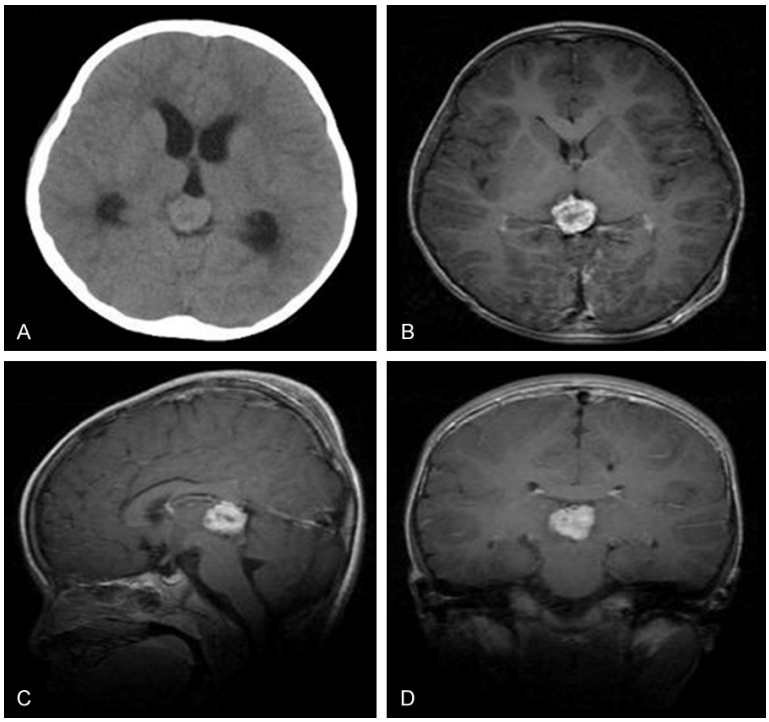

Figure 1. A: The tumor was located at posterior third ventricle and showed isodense on CT scan. B-D: MRI showed slight hypointense on T1-weighted sequences and displayed a strong contrast enhancement.

Alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG) level may support the diagnosis of embryonal carcinoma. AFP is produced by the yolk sac in the early stage of development and HCG is synthesized by the chorioepithelium. Embryonal carcinoma contains multiple differentiated extraembryonic structures. It also produces produce both AFP and HCG. Elevation of these two may be considered for the diagnosis of embryonal carcinoma [12-20]. Embryonal carcinoma is considered the most histogenetically primitive of the germ cell tumors and has the potential to differentiate into mature or immature teratoma. Histologically, this tumor consists of anaplastic columnar to cuboidal cells [21, 22].

Surgery combined with intensive postoperative radiotherapy and chemotherapy is the treatment modalities for embryonal carcinoma [1]. However, the patient survival rate is very low for embryonal carcinoma; the median survival was less than 2 years whereas for the 5 years survival rate was less than 25% [23, 24]. We present 2 cases of intracranial embryonal carcinoma from our center and 13 cases from other literatures. The clinical findings, radiologic findings, surgical treatment and outcomes were summarized to diagnose and consider the treatment modalities for these rare lesions.

Clinical materials and results

There were 13 cases which had been reported previously in which the clinical results of each case have been described in the literatures [4, 5, 7, 13, 25-31] and our 2 cases in this report were reviewed (**Table 1**). All patients were verified histologically as pure embryonal carcinoma. Six Collective studies from other institutions [1, 23, 32-35] were reviewed (**Table 2**) for comparative study. We analyzed the outcome and treatment strategy to clarify the best combination treatment which can provide better

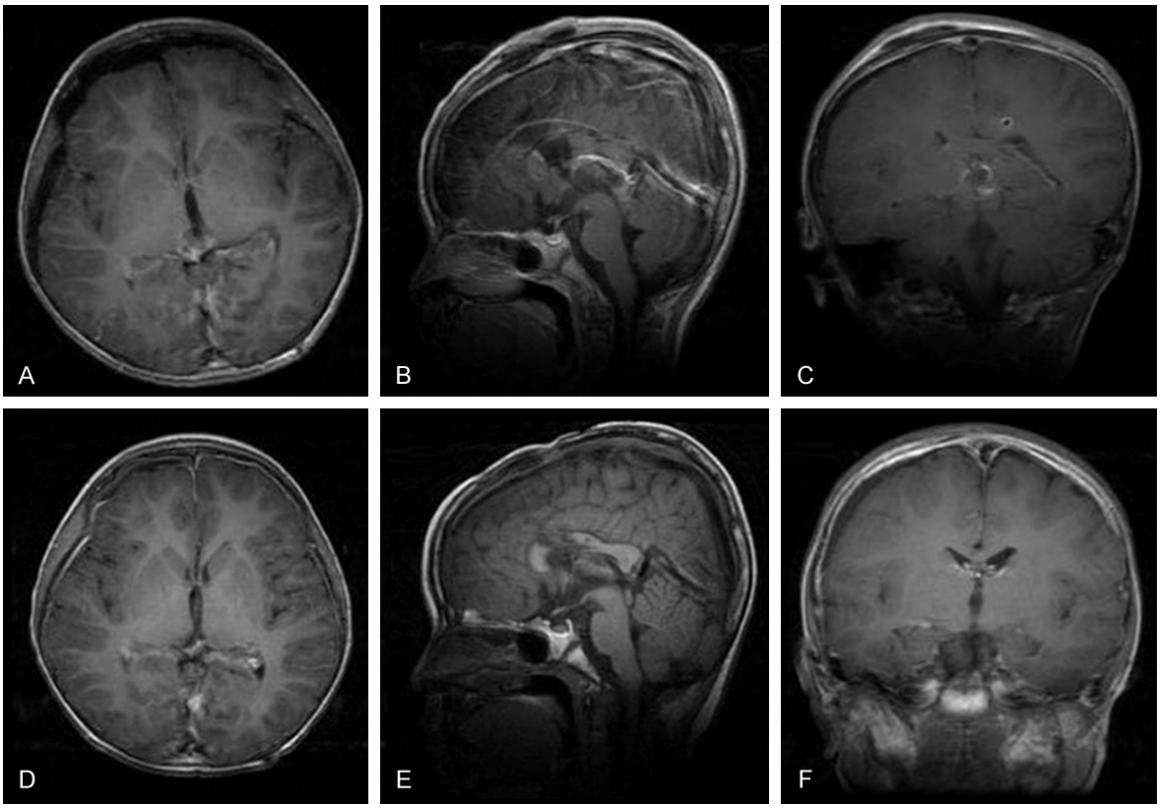

Figure 2. A-C: Postoperative MRI scans showing subtotal removal of the mass lesion in 5 years old patient. D-F: MRI scans 6 months after operation showed no recurrence of the tumor.

prognosis result. Data from 15 reported cases of pure embryonal carcinoma showed that most of the patients have poor prognosis. There were only 3 cases which have survived more than 20 months. In most of cases, patients died within 1 year due to tumor recurrence although they had combination treatment (surgery, radiotherapy and chemotherapy).

Case reports

Case 1

A 5-year-old girl was admitted to our hospital in June 2012 with a 3 days history of paroxysmal headache, nausea and vomiting. The headache was described as dull headache, with no projectile vomiting. Patient had no seizures, no paresis on extremities, or loss of consciousness before admission. Neurologic examination was normal, and funduscopic exploration disclosed a papilledema bilaterally.

CT imaging revealed an isodense posterior third ventricular mass which was responsible for the occlusion of the aqueduct of midbrain and secondary ventricular hydrocephalus. MRI delineated the tumor better, which was located at the posterior third ventricle, with slight hypointense on T1-weighted sequences and displayed strong contrast enhancement [**Figure 1**]. Cerebrospinal fluid evaluation demonstrated normal levels of α-fetoprotein (AFP; < 0.605 ng/ml) and human chorionic gonadotropin (HCG; 0.29 IU/l). Blood serum evaluation also demonstrated normal levels of α-fetoprotein (AFP; < 0.605 ng/ml) and human chorionic gonadotropin (HCG; 0.1 IU/l).

A ventriculoperitoneal shunting was performed in emergency with immediate postoperative relief. Subsequently, a subtotal surgical resection was achieved via an interhemispheric transcallosal interforniceal approach. During operation, the tumor was found to be yellowish red solid tumor with calcification; the tumor texture was both soft and tenacious. The tumor had rich blood supply and was quite adhered with surrounding tissue with less clear boundaries. Part of the tumor was tightly adhered with vein of Galen. Tumor specimens showed a

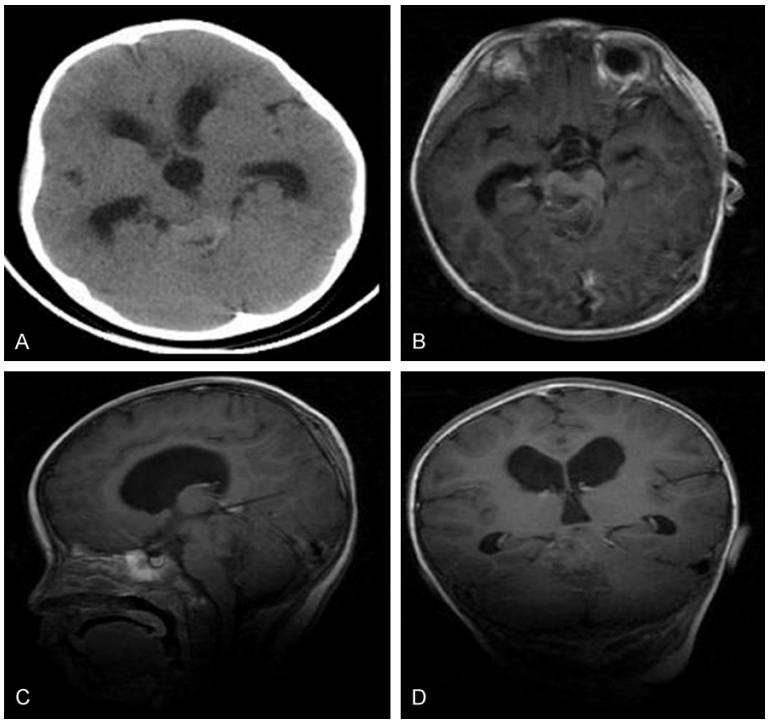

Figure 3. A: CT imaging revealed an isodense pineal area mass lesion, but there is slight hyperdense in it. B-D: MRI showed isointense to slight hypointense on T1-weighted sequences and displayed a heterogeneous contrast enhancement.

histologically aggressive tumor containing epithelial primitive cells forming solid sheets and rare glandular formations [**Figure 6**]. Immunohistochemical staining was positive for OCT3/4, CD30, CK, Ki-67 [**Figure 7**]. Based on the typical microscopic findings, the tumor was considered as a pure embryonal carcinoma. Adjuvant high-dose cisplatin-based chemotherapy was administered postoperatively. Later, the patient also had postoperative radiotherapy.

Postoperative MRI scans showed a little tumor remnants [**Figure 2A**], and the patient had been symptom-free with no clinical or radiological sign of progression at follow-up examination, 6 months after surgery. Unfortunately, the patient died eventually from a pleural effusion caused by lung metastasis of the tumor. Head MRI showed no local tumor recurrence [**Figure 2B**].

Case 2

A 2-year-old girl was admitted to our hospital in June 2012 with a 1 month history of head tilted to the left and exotropia on the left eye. Patient had headache and vomiting, no seizures, no paresis on extremities or loss of consciousness before admission.

CT imaging revealed an isodense in most of the mass, but there is slight hyperdense in it. The mass was located in the pineal area and responsible for the occlusion of the aqueduct of the midbrain and secondary ventricular hydrocephalus. MRI delineated the tumor better, which was located at the pineal area extended to fourth ventricle; with isointense to slight hypointense on T1-weighted sequences and displayed heterogeneous contrast enhancement [**Figure 3**], and T2-weighted image showed intratumoral-hemorrhage-like signal [**Figure 5A**]. Systemic and cerebrospinal fluid evaluation demonstrated normal levels of α-fetoprotein (AFP; 3 ng/ml). Blood serum evaluation also demonstrated normal levels of α-fetoprotein (AFP; 2.51 ng/ml) and human chorionic gonadotropin (HCG; < 1 IU/l).

A ventriculoperitoneal shunting was performed in emergency with immediate postoperative relief. Subsequently, a subtotal surgical resection was achieved via an infratentorial supracerebellar approach. During operation, the tumor was found to be grayish red solid tumor; the tumor texture was both soft and tenacious. The tumor was extended from tegmentum of the midbrain to the fourth ventricle; the tumor had rich blood supply and the tumor was quite adhered with surrounding tissue with less clear boundaries.

Tumor specimens showed a histologically aggressive tumor containing epithelial primitive cells forming solid sheets and glandular formations. Immunohistochemical staining was positive for OCT3/4, CD30, CK, Ki-67, and the tumor was considered as a pure embryonal carcinoma. Postoperative MRI scans showed a little tumor remnants [**Figure 4**]. Patient did not have

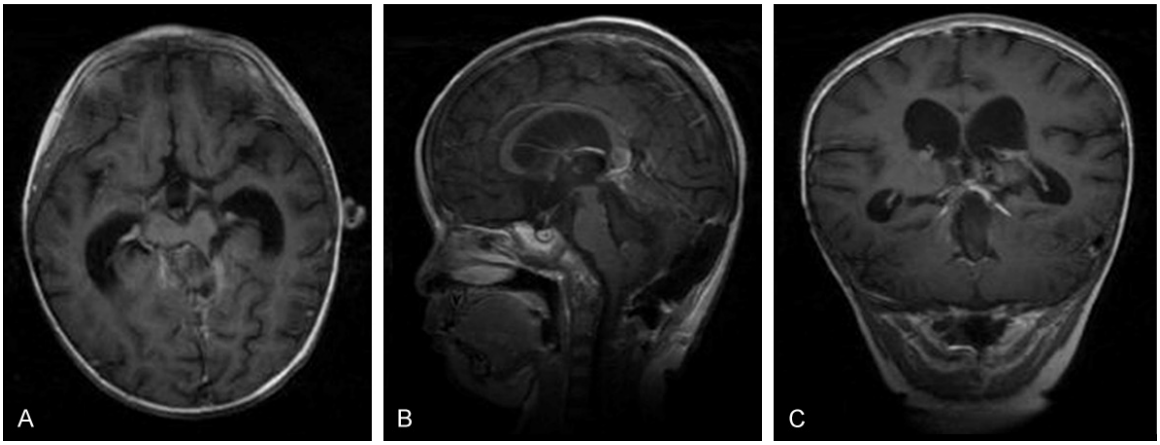

Figure 4. Postoperative MRI scans showing subtotal removal of the mass lesion in 2 years old patient.

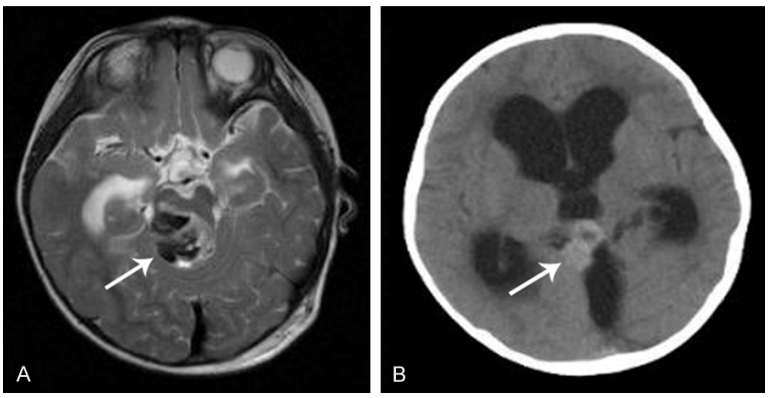

Figure 5. A: T2-weighted image showed intratumoral-hemorrhage-like signal. B: Postoperative CT scan revealed tumor recurrence after 3 months in 2 years old patient.

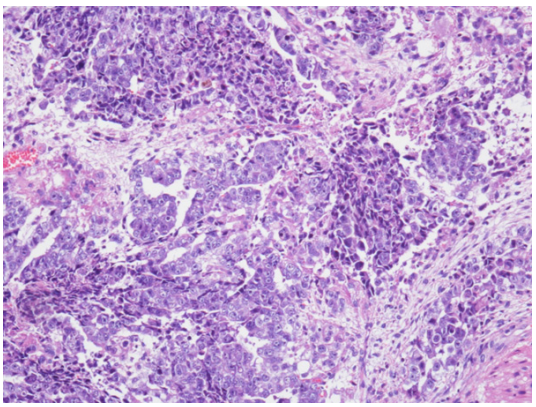

Figure 6. A histologically aggressive tumor containing epithelial primitive cells forming solid sheets and rare glandular formations (H&E staining, 100×).

adjuvant chemotherapy and radiotherapy. Postoperative MRI scans after 3 months showed local tumor recurrence [**Figure 5B**], and the patient died 6 months after surgery. The cause of death is tumor recurrence.

Discussion

Embryonal carcinoma is a rare malignant intracranial neoplasm. Embryonal carcinomas was first reported by Nishiyama et al and subsequently by Borit et al; the usual locations are tuber cinereum, third ventricle, infundibular region, optic chiasma, suprasellar and intrasellar regions [36, 37]. The theory for embryonal carcinoma origin is remained unclear. In 1946, Friedman and Moore concluded that tumor arises from primordial germ cells that should be called germinomas, and in the following years, they proposed that the embryonal carcinoma was developed from germinoma. According to Dixon and Moore, germ cells gave rise to the germinoma and, alternatively, to the embryonal carcinoma from which the choriocarcinoma and teratoma were derived. Later, Teilum et al summed up the so-called germ cell theory. Germ cell theory explained that germ cells gave rise to germinomas and tumors composed of totipotential cells that gave rise to embryonal carcinomas. This theory also stated that endodermal sinus tumors, choriocarcinomas and teratomas were derived from embryonal carcinomas. Later, this theory was approved by Rubenstein and the World Health Organization committee on brain tumor classifi-

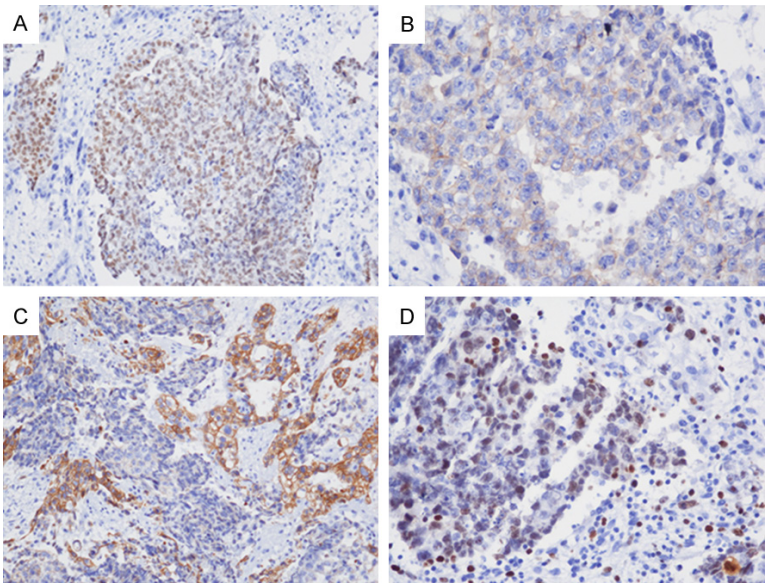

Figure 7. Immunohistochemical staining was positive for (A) OCT3/4; (B) CD30; (C) CK; (D) Ki-67.

cation. In 1974, Khantanaphar et al first reported embryonal carcinoma located in the cerebellum. This finding revealed another possibility that the germ cells may migrate through certain tissues before arriving at the gonadal region [4, 38-43]. In 1999, Sano et al proposed another hypothesis, contrary to the above theory. The hypothesis recommended that germ cell tumor is not attributed to one single origin which was the primordial germ cells. According to Sano et al, embryonal carcinoma may arise from the misinvolved-misenfolded cells in earlier stages of embryogenesis (ontogenesis); which was also stated by Matsutani et al [23, 33]. In 2013, Tan and Scotting suggested a novel hypothesis that this tumor arose from the transformation of endogenous brain cells, although future study is needed for clarification [44].

Embryonal carcinoma usually occurs in adolescence and young adult population. Jennings et al suggested that the changes at the time of puberty might induce malignant behavior in germ cells residing in the diencephalopineal region. Thus, gonadotropins would act as transforming agents in this pubertal population. We reported two cases of embryonal carcinoma, both occurred in prepubertal region. Perhaps in this case, the precursor cells required only low level exposure to gonadotropins for transformation; this consideration remains speculative and needs further study to see the gonadotropins relation with this tumor [1].

MRI and CT remain a useful technique for the initial screening, but none of these features could be found to differentiate among germinoma, choriocarcinoma, embryonal carcinoma and yolk sac tumor in the pineal region. Embryonal carcinoma, like most of other germ cell tumors, tends to appear denser than the surrounding brain on the pre- and post-contrast CT scan, and enhances brightly and homogenously more often than heterogeneously. Chang et al reported that no calcification was noted in embryonal carcinoma [27, 45, 46]. The CT findings in our reported case is inconsistent with above statement; the CT scan results showed isodense and slight hyperdense on pre-contrast CT, and no significance calcification was found. However, there was an interesting finding during operation; we found a small calcification inside the tumor. This is quite unique because most of the calcification can be seen on CT scan. MRI revealed slight hypointense on T1-weighted sequences and both homogenous and heterogeneous contrast enhancement. In one of our cases, the T2-weighted sequences showed intratumoral-hemorrhage-like appearances; this might be a consideration that tumor stroke might occur in embryonal carcinoma since it had rich blood supply.

Increasing level of AFP and HCG may help the diagnosis of this tumor, as reported by many literatures [13-19]. Ushio et al and Matsutani et al also reported high serum levels of AFP and HCG in embryonal carcinoma patient [23, 32]. Inconsistent with these literatures, we found that the CSF and blood serum level of AFP and HCG in our case were normal; our results were consistent with literature reported by Nsir et al. Here we suggested another hypothesis that the elevation of AFP and HCG have relation with age or pre-, during or post puberty condition. We considered this because both patients in our case report were in pediatric population

and the AFP and HCG level were normal at admission. As from this data we thought that AFP and HCG level in children embryonal carcinoma might be different with the young and adult population. Further study needs to be done, including retrospective and collective study, to answer this question. AFP and HCG level alone cannot confirm the diagnosis for embryonal carcinoma. However, these are important to consider whether preoperative chemotherapy and radiotherapy should be given. We had recommended for patients in our institution diagnosed with other types of germ cell tumors whom have elevation in AFP and HCG to have preoperative chemotherapy and radiotherapy; the result was both AFP and HCG level were decreasing after the treatment, and it's consistent with other reported literatures [47].

Hydrocephalus and Parinaud's syndrome generally present in posterior third ventricle and pineal area tumor. Two patients in our cases were presented with hydrocephalus and we performed ventriculoperitoneal shunt prior to surgery to relieve the intracranial pressure; one of the patients had Parinaud's syndrome. The placement of ventriculoperitoneal shunt might benefit surgical treatment. In high intracranial pressure condition, rapid drop of the blood pressure and cerebral or cerebellar bulging may occur during surgery and sudden decompression after dural opening might increase the surgical morbidity and mortality. Surgical approach might include occipital transtentorial or frontal transcallosal; infratentorial supracerebellar approach is generally used in patients with pineal tumors, and the pterional of subfrontal approach is preferred in patients with sellar region tumors. For posterior third ventricle and pineal region, most of the tumor has intimate relationship with the posterior thalamus and deep cerebral veins, such as internal cerebral veins and vein of Galen. Because of this complex anatomical structure, we do not recommend any stereotactic biopsy. Despite its disadvantageous location, the tumor mostly had a clear anatomic boundary with surrounding normal tissue so in most cases subtotal to total resection can be achieved [48-51]. In our presented cases we performed transcallosal approach for the tumor located in the posterior third ventricle and infratentorial supracerebral approach for tumor located in pineal area extended to the fourth ventricle. Under surgical microscope, the tumor had less clear boundaries and tightly adhered with surrounding normal tissue which had rich blood supply. We achieved subtotal resection in both our cases. CD30-positive staining basically can confirm the diagnosis of embryonal carcinoma, but evidence from recent studies showed that new immunostains such as organic cation transporter 3/4 (OCT3/4) had a better sensitivity and specificity than CD30 [52, 53]. In our case, the combination of specific microscopic findings, OCT3/4, CD30, CK and Ki-67 positively led to the diagnosis of pure embryonal carcinoma.

The efficacy of radiotherapy and chemotherapy remains a topic of controversy. Nevertheless, most patients still receive those treatments. The tumor may extend via three different pathways: direct continuity, seeding via the CSF and occasionally via the blood stream. Whole radiotherapy can be considered because of the malignant characteristic of the tumor that disseminate through CSF; chemotherapy might be considered in patient who has a delayed craniospinal irradiation or in average risk patients, and in young patients especially less than 3 years old [45, 54, 55]. Besides, adjuvant chemotherapy might reduce the radiotherapy doses. The usual chemotherapy regimen which is generally used in NGGCT is PVB (cisplatin/vinblastine/bleomycin) combination. Robertson et al reported that the 4 year progression-free survival rate was 67% [34]. German/Italian pilot study treated 19 NGGCT patients with neoadjuvant chemotherapy (cisplatin/etoposide/ifosfamide) followed by radiation therapy. Preliminary results revealed an 81% progression-free survival rate at 12 months. Jennings and Balcameda attempted to use single-modality therapy with radiation therapy alone or chemotherapy alone; the results were at unacceptably high recurrence rate [1, 35, 36]. French pilot study used 6 cycles of multiagent chemotherapy alone and deferral of radiotherapy; the results were relapse of the tumor [56]. Later, a study conducted by Japanese Intracranial Germ Cell Tumor Study Group using PE (cisplatin and etoposide) had showed promising result for primary intracranial germ cell tumors. Based on this result, Ushio et al [32] applied the PE therapy preoperatively in combination with radiotherapy in primary intracranial yolk sac tumors or embryonal carcinoma. The objectives of this

therapy are to reduce the tumor volume, therefore minimizing the side effects of surgery, and decrease the viability of tumor cells to prevent CSF metastasis. The result of this study was identical to that reported by Robertson et al [34]. On the contrary, Matsutani et al showed that embryonal carcinoma patient had 3 year survival rate of 27.3%; less than the result reported by Ushio and Robertson. Matsutani reported that extensive surgery might be beneficial to reduce the recurrence, compared to partial removal, and chemotherapy was not significantly more effective than radiation therapy alone [23, 57]. In our cases, both patients did not have good prognosis; one of the patient died 1 year after surgery combined with postoperative cisplatin-based chemotherapy and radiotherapy. The other patient had worse prognosis and due to the patient's age of younger than 3 years old, we did not recommend chemotherapy and radiotherapy; the patient died 6 months later due to local recurrence of the tumor. Our reported case is consistent with Matsutani report.

Disclosure of conflict of interest

None.

Address correspondence to: Chunde Li, Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China. Tel: +86-13366077663; E-mail: lichunde@hotmail.com

References

[1] Jennings MT, Gelman R and Hochberg F. Intracranial germ-cell tumors: natural history and pathogenesis. J Neurosurg 1985; 63: 155-167.

[2] Liang L, Korogi Y, Sugahara T, Ikushima I, Shigematsu Y, Okuda T, Takahashi M, Kochi M and Ushio Y. MRI of intracranial germ-cell tumours. Neuroradiology 2002; 44: 382-388.

[3] Rosenblum MK and Ng HK. Tumours of the nervous system. Lyon: international agency for research on cancer; 1997.

[4] Khantanaphar S and Bunyaratvej S. Embryonal carcinoma in the cerebellum. Case report. J Neurosurg 1974; 40: 657-662.

[5] Koeleveld RF and Cohen AR. Primary embryonal-cell carcinoma of the parietal lobe. Case report. J Neurosurg 1991; 75: 468-471.

[6] Ono N, Inoue HK, Naganuma H, Kunimine H, Zama A and Tamura M. Diagnosis of germinal neoplasm in the thalamus and basal ganglia. Surg Neurol 1986; 26: 24-28.

[7] Ben Nsir A, Darmoul M, Hadhri R, Zemmali M and Hattab N. Primary pure and nonsecreting embryonal carcinoma of the anterior third ventricle: a case report. Pediatr Neurosurg 2015; 50: 76-79

[8] Edwards MS, Hudgins RJ, Wilson CB, Levin VA and Wara WM. Pineal region tumors in children. J Neurosurg 1988; 68: 689-697.

[9] Jellinger K. Primary intracranial germ cell tumours. Acta Neuropathol 1973; 25: 291-306.

[10] Malogolowkin MH, Mahour GH, Krailo M and Ortega JA. Germ cell tumors in infancy and childhood: a 45-year experience. Pediatr Pathol 1990; 10: 231-241.

[11] Rueda-Pedraza ME, Heifetz SA, Sesterhenn IA and Clark GB. Primary intracranial germ cell tumors in the first two decades of life. A clinical, light-microscopic, and immunohistochemical analysis of 54 cases. Perspect Pediatr Pathol 1987; 10: 160-207.

[12] Allen JC, Nisselbaum J, Epstein F, Rosen G and Schwartz MK. Alphafetoprotein and human chorionic gonadotropin determination in cerebrospinal fluid. An aid to the diagnosis and management of intracranial germ-cell tumors. J Neurosurg 1979; 51: 368-374.

[13] Arita N, Ushio Y, Abekura M, Koshino K and Hayakawa T. Embryonal carcinoma with teratomatous elements in the region of the pineal gland. Surg Neurol 1978; 9: 198-202.

[14] Haase J and Borgaard-Pedersen B. Alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG) as biochemical markers of intracranial germ-cell tumours. Acta Neurochir 1979; 50: 67-69.

[15] Jordan RM, Kendall JW, McClung M and Kammer H. Concentration of human chorionic gonadotropin in the cerebrospinal fluid of patients with germinal cell hypothalamic tumors. Pediatrics 1980; 65: 121-124.

[16] Norgaard-Pedersen B, Lindholm J, Albrechtsen R, Arends J, Diemer NH and Riishede J. Alphafetoprotein and human chorionic gonadotropin in a patient with a primary intracranial germ cell tumor. Cancer 1978; 41: 2315-2320.

[17] Perlin E, Engeler JE Jr, Edson M, Karp D, McIntire KR and Waldmann TA. The value of serial measurement of both human chorionic gonadotropin and alpha-fetoprotein for monitoring germinal cell tumors. Cancer 1976; 37: 215-219.

[18] Sun MJ, Qang YC and Liu MY. Alpha-fetoprotein, human chorionic gonadotropin and carcinoembryonic antigen in pineal region tumors. Chinese Med J 1986; 272-279.

[19] Takeuchi J, Handa H, Oda Y and Uchida Y. Alpha-fetoprotein in intracranial malignant teratoma. Surg Neurol 1979; 12: 400-404.

[20] Yoshida K, Toya S, Ohtani M, Okui S, Takenaka N and Harigaya K. Extraneural metastasis of

choriocarcinomatous element in pineal germ-cell tumor. Case report. J Neurosurg 1985; 63: 463-466.
[21] Bjornsson J, Scheithauer BW, Okazaki H and Leech RW. Intracranial germ cell tumors: pathobiological and immunohistochemical aspects of 70 cases. J Neuropathol Exp Neurol 1985; 44: 32-46.
[22] Chang CG, Kageyama N, Kobayashi T, Yoshida J and Negoro M. Pineal tumors: clinical diagnosis, with special emphasis on the significance of pineal calcification. Neurosurgery 1981; 8: 656-668.
[23] Matsutani M, Sano K, Takakura K, Fujimaki T, Nakamura O, Funata N and Seto T. Primary intracranial germ cell tumors: a clinical analysis of 153 histologically verified cases. J neurosurg 1997; 86: 446-455.
[24] Rich TA, Cassady JR, Strand RD and Winston KR. Radiation therapy for pineal and suprasellar germ cell tumors. Cancer 1985; 55: 932-940.
[25] Maeda Y, Mabuchi E, Koyama T, Kano M and Arita N. A case of embryonal carcinoma arising in the basal ganglia of the cerebrum. No Shinkei Geka 1990; 18: 675-680.
[26] Nakajima F, Pak S, Fujitsu K and Kuwabara T. A case of alpha-fetoprotein producing primary intracranial embryonal carcinoma treated with combination chemotherapy with cis-platinum, vinblastine and bleomycin. No Shinkei Geka 1981; 9: 371-375.
[27] Packer RJ, Sutton LN, Rorke LB, Rosenstock JG, Zimmerman RA, Littman P, Bilaniuk LT, Bruce DA and Schut L. Intracranial embryonal cell carcinoma. Cancer 1984; 54: 520-524.
[28] Marshall LF, Rorke LB and Schut L. Teratocarcinoma of the brain - a treatable disease?. Childs Brain 1979; 5: 96-102.
[29] Sakata K, Yamada H, Sakai N, Hosono Y, Kawasako T and Sasaoka I. Extraneural metastasis of pineal tumor. Surg Neurol 1975; 3: 49-54.
[30] Wang JN, Lin SJ, Chio CC and Liu HM. Suprasellar embryonal carcinoma: report of one case. Zhonghua Minguo Xiao Er Ke Yi Xue Hui Za Zhi 1995; 36: 438-441.
[31] Sasaoka Y, Kamada K, Nakaue Y, Hujimoto T, Bessho H, Tunoda S and Sakaki T. [Cisplatin-etoposide chemotherapy of an embryonal carcinoma arising in the basal ganglia of the cerebrum: a case report]. No Shinkei Geka 1994; 22: 631-636.
[32] Ushio Y, Kochi M, Kuratsu J, Itoyama Y and Marubayashi T. Preliminary observations for a new treatment in children with primary intracranial yolk sac tumor or embryonal carcinoma. Report of five cases. J Neurosurg 1999; 90: 133-137.
[33] Sano K. Pathogenesis of intracranial germ cell tumors reconsidered. J Neurosurg 1999; 90: 258-264.
[34] Robertson PL, DaRosso RC and Allen JC. Improved prognosis of intracranial non-germinoma germ cell tumors with multimodality therapy. J Neuro Oncol 1997; 32: 71-80.
[35] Calaminus G, Andreussi L, Garre ML, Kortmann RD, Schober R and Gobel U. Secreting germ cell tumors of the central nervous system (CNS). First results of the cooperative German/Italian pilot study (CNS sGCT). Klin Padiatr 1997; 209: 222-227.
[36] Borit A. Embryonal carcinoma of the pineal region. J Pathol 1969; 97: 165-168.
[37] Nishiyama RH, Batsakis JG, Weaver DK and Simrall JH. Germinal neoplasms of the central nervous system. Arch Surg 1966; 93: 342-347.
[38] Dixon FJ and Moore RA. Testicular tumors; a clinicopathological study. Cancer 1953; 6: 427-454.
[39] Friedman NB. Germinoma of the pineal; its identity with germinoma (seminoma) of the testis. Cancer Res 1947; 7: 363-368.
[40] Friedman NB. The comparative morphogenesis of extragenital and gonadal teratoid tumors. Cancer 1951; 4: 265-276.
[41] Rubinstein LJ. Cytogenesis and differentiation of pineal neoplasms. Hum Pathol 1981; 12: 441-448.
[42] Teilum G. Endodermal sinus tumors of the ovary and testis. Comparative morphogenesis of the so-called mesoephroma ovarii (Schiller) and extraembryonic (yolk sac-allantoic) structures of the rat's placenta. Cancer 1959; 12: 1092-1105.
[43] Teilum G. Classification of endodermal sinus tumour (mesoblatoma vitellinum) and so-called "embryonal carcinoma" of the ovary. Acta Pathol Microbiol Scand 1965; 64: 407-429.
[44] Tan C and Scotting PJ. Stem cell research points the way to the cell of origin for intracranial germ cell tumours. J Pathol 2013; 229: 4-11.
[45] Chang T, Teng MM, Guo WY and Sheng WC. CT of pineal tumors and intracranial germ-cell tumors. Am J Roentgenol 1989; 153: 1269-1274.
[46] Zimmerman RA, Bilaniuk LT, Wood JH, Bruce DA and Schut L. Computed tomography of pineal, parapineal, and histologically related tumors. Radiology 1980; 137: 669-677.
[47] Matsukado Y, Abe H, Tanaka R, Kobayashi T, Yamashita J, Nishimoto A, Ushio Y, Sato K, Matsutani M and Takakura K. [Cisplatin, vinblastine and bleomycin (PVB) combination chemotherapy in the treatment of intracranial malignant germ cell tumors--a preliminary report of a phase II study--The Japanese Intracranial

Germ Cell Tumor Study Group]. Gan No Rinsho 1986; 32: 1387-1393.
[48] Messina AV, Potts G, Sigel RM and Liebeskind AL. Computed tomography: evaluation of the posterior third ventricle. Radiology 1976; 119: 581-592.
[49] Rout D, Sharma A, Radhakrishnan VV and Rao VR. Exploration of the pineal region: observations and results. Surg Neurol 1984; 21: 135-140.
[50] Chapman PH and Linggood RM. The management of pineal area tumors: a recent reappraisal. Cancer 1980; 46: 1253-1257.
[51] Stein BM. The infratentorial supracerebellar approach to pineal lesions. J Neurosurg 1971; 35: 197-202.
[52] Iczkowski KA, Butler SL, Shanks JH, Hossain D, Schall A, Meiers I, Zhou M, Torkko KC, Kim SJ and MacLennan GT. Trials of new germ cell immunohistochemical stains in 93 extragonadal and metastatic germ cell tumors. Hum Pathol 2008; 39: 275-281.
[53] Looijenga LH, Stoop H, de Leeuw HP, de Gouveia Brazao CA, Gillis AJ, van Roozendaal KE, van Zoelen EJ, Weber RF, Wolffenbuttel KP, van Dekken H, Honecker F, Bokemeyer C, Perlman EJ, Schneider DT, Kononen J, Sauter G and Oosterhuis JW. POU5F1 (OCT3/4) identifies cells with pluripotent potential in human germ cell tumors. Cancer Res 2003; 63: 2244-2250.
[54] Bouffet E. Embryonal tumours of the central nervous system. Eur J Cancer 2002; 38: 1112-1120.
[55] Foo AS, Lim C, Chong DQ, Tan DY and Tham CK. Primary intracranial germ cell tumours: experience of a single South-East Asian institution. J Clin Neurosci 2014; 21: 1761-1766.
[56] Baranzelli MC, Patte C, Bouffet E, Portas M, Mechinaud-Lacroix F, Sariban E, Roche H and Kalifa C. An attempt to treat pediatric intracranial alphaFP and betaHCG secreting germ cell tumors with chemotherapy alone. SFOP experience with 18 cases. Societe Francaise d'Oncologie Pediatrique. J Neuro Oncol 1998; 37: 229-239.
[57] Matsutani M, Takakura K and Sano K. Primary intracranial germ cell tumors: pathology and treatment. Prog Exp Tumor Res 1987; 30: 307-312.