Original Article Intracranial embryonal carcinoma: a clinicopathologic study of ten cases and review of the literature

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Abstract: Objective: Embryonal carcinoma (EC) is an uncommon subtype of intracranial germ cell tumors. The aim of this study is to determine the clinical characteristics and prognosis of EC. Methods: A total of ten EC patients were underwent surgical treatment. Three patients gained total resection (TR) and seven gained subtotal resection (STR). Radiotherapy was provided in nine patients and chemotherapy was provided in eight patients. Their clinical data, radiological, histopathological features and postoperative follow-up were analyzed retrospectively. Results: All ten patients had follow-up with a median follow-up period of 23.5 months. The pineal gland was the most common site (n=6) and headache was the most common symptom (n=6). Highly elevated alpha fetoprotein (AFP) and beta sub-unit human chorionic gonadotropin (β -HCG) were recorded in seven and one patient, respectively. The tumor cells have a relatively high MIB-1 labeling index ranging from 40% to 90% by immunohistochemical staining. The median overall survival (OS) time for EC with TR compared to STR was 35 months to 20 months (*P*=0.49). Conclusions: EC is a rare subtype of intracranial germ cell tumors with a tendency to present in younger patients and has a male bias. EC has a poor prognosis. The extent of resection is an important prognosis factor. More data should be collected in order to evaluate the role of the AFP in diagnosing the EC and predicting the prognosis.

Keywords: Embryonal carcinoma, intracranial, germ cell tumors, tumor maker, surgery, prognosis

Introduction

Intracranial germ cell tumors (GCTs) are relatively rare tumors. Their incidence has been considered to be higher in East Asia than in the United States. In far-east Asia, central nervous system (CNS) GCTs account for 2-3% of primary intracranial neoplasms, and for 8-15% of specifically pediatric examples, in series from Japan, Taiwan and Korea [1-3]. In the West, these neoplasms constitute only 0.3-0.6% of primary intracranial neoplasms and approximately 3-4% of those affecting children [4-6]. They are classified into six different variants according to the 2007 World Health Organization (WHO) classification for brain tumors [7]. European studies classify GCTs as germinoma and non-germinomatous GCTs [8, 9], the latter include teratoma, embryonal carcinoma (EC), yolk sac tumor, choriocarcinoma and mixed GCTs. Germinoma accounts for approximately 50%-70% of cases and non-germinomatous GCTs make up the remaining third [9]. EC is an uncommon subtype of intracranial GCTs with an incidence of only 1.8-5.0% of primary intracranial GCTs [2, 3, 9]. Most of ECs are described as isolated case reports and previous reports have not systemically described the clinical features and prognosis of ECs. Due to the rarity, EC might be underdiagnosed and the clinical diagnosis, treatment protocol and prognosis are still uncertain. Here, we present a clinicopathologic study of ten cases of intracranial ECs. To the best of our knowledge, this is the largest case series in the existing literature.

Material and methods

Patients

All of the patients received surgical treatment between January 1995 and December 2010 at Xinhua Hospital, School of Medicine, Shanghai Jiaotong University, China and Anhui Provincial Hospital, Anhui Medical University, China. Clinical data, including sex, age, clinical symptoms, duration of symptoms, tumor location, laboratory reports, operative findings and adjuvant therapy, were obtained from the medical records and follow-up. The diagnosis of EC required microscopic and immunohistochemical evidence, as identified by two experienced neuropathologists (YL Wang and MJ Zhu), who had no prior knowledge of the clinical status of the patients and re-examined the tumor samples using the 2007 WHO classification [7].

Histological examination and immunohistochemical staining

Among this group, six cases of EC were from Xinhua Hospital and the other four cases were from Anhui Provincial Hospital. All ten patients were treated with surgical resection of the tumor. All the specimens had been fixed in 10% buffered formalin and submitted for routine processing and paraffin embedding. Hematoxylin and eosin (H&E) was performed by routine methods. For all cases, the following immunohistochemical stains with their respective antibody dilutions were performed on paraffinembedded tissue: CK (1:100), CD30 (1:100), octamer binding factor 3/4 (OCT-3/4) (1:100), placental alkaline phosphatase (PLAP) (1:100), elevated alpha fetoprotein (AFP) (1:100), beta subunit human chorionic gonadotropin (β-HCG) (1:100) and MIB-1 (1:100). All of the antibodies were obtained from M/S Dako (Glostrup, Denmark). Appropriate positive and negative controls for each antibody were run in parallel. All counts were performed at a magnification of × 400 (field size, 0.16 mm²), and five viable fields from the area of maximum labeling were chosen for counting. Distinct nuclear MIB-1 staining of the tumor cell was recorded as positive. The MIB-1 labeling index (MIB-1 LI) was calculated as the percentage of MIB-1-positive tumor cells in the evaluated area. Vascular components and hematogenous cells were excluded, and evaluated areas also excluded necrotic, degenerate and poorly preserved areas.

Follow-up and ethical committee approval

The patients' prognoses were obtained from clinical observation. The surgical procedures and clinical follow-up were conducted under the guidelines and terms of all relevant local legislation and received approval from the ethics committee of Shanghai Jiaotong University and Anhui Medical University, China.

Statistical analysis

The potential prognostic factors of tumor makers and extent of resection were analyzed. The overall survival (OS) was calculated for each category among the ten patients with known living status at the end of the study. Survival probabilities were calculated according to the Kaplan-Meier method and were measured from the date of diagnosis to the date of death. Bivariate associations between survival and the selected prognostic factors were tested using the log-rank test, and multivariate associations were not assessed for the limitation of little number of cases. A two-sided probability level of 0.05 was chosen for statistical significance. Statistical analysis was performed with SPSS for Windows (version 18.0; SPSS, Chicago, IL, USA).

Results

Clinical features

This series included nine males and one female, with a median age of 12.5 years (range: 13 months to 26 years; five were \leq 12 years) upon initial diagnosis. The most common presenting symptom was headache (n=6). Other symptoms included diplopia (n=2), dizziness (n=1), and polyuria (n=1). The duration of the symptoms varied from two weeks to eighteen months with a median period of three months.

Nine cases were solitary tumors, and one case was multiple tumors on the initial diagnosis. The tumor occurred in different locations, and the pineal gland was the most common site (n=6); other tumor locations included the suprasellar region (n=1), both the pineal and the suprasellar region (n=1), the slope (n=1), and the third ventricle (n=1) on the initial operation. The tumors of the ten patients on the initial diagnosis ranged in size from 15 to 40 mm (median: 30 mm) in maximal diameter.



Figure 1. (A) 13-month-old girl presenting with headache and vomiting. Non-enhanced CT image (A) shows isodense lesion located in the pineal region, the third ventricle is compressed, and the obstructive hydrocephalus is also illustrated. Unenhanced MR images show a round, well-defined mass in the pineal region; the mass is low-intensity signal on T1-WI (B), and iso-intensity signal on T2-WI (C), with moderate edema and mass effect. Axial (D), coronal (E) and sagittal (F) T1-weighted MR images show the mass enhances strongly and heterogeneously after the administration of Gd-based contrast agent.

Surgical tumor removal was performed in all the ten patients. On the initial surgery, total resection (TR) was attained in three surgeries, and subtotal resection (STR) was attained in seven surgeries. Salvage operation was performed in two patients, and STR was attained. Additional radiotherapy was provided in nine patients and chemotherapy was performed in eight patients. One case was less than thirtysix months on the initial operation, and radiotherapy was not performed in view of the side effect on the cerebrum and spinal cord. In our institution, involved-field radiotherapy was then applied four weeks after completion of surgery with the use of a dose of 60 Gy in 30 fractions, at 2 Gy/fraction over six weeks. The patients tolerated the entire treatment well in the series.

Radiological findings

Plain computed tomography (CT) data were available in eight cases. CT scan showed isodense (n=5) or slightly hyperdense (n=3) masses. Calcification was found in two cases. Magnetic resonance imaging (MRI) data were available in all the ten cases. The tumors were isointense (n=5) or hypointense (n=5) on T1-weighted imaging and isointense (n=5) or hyperintense (n=5) on T2-weighted imaging. All the cases showed strongly heterogeneous (n=5) or homogeneous (n=5) enhancement after administration of gadolinium. The masses had oval or irregular shape. Distinct boundary was found in seven lesions and cysts were seen in three lesions. Five patients showed expanded ventricular system. Two patients had intracranial dissemination on recurrence. The radiological pictures of case 10 were shown in Figure 1.

Tumor makers

The pre-operative serum titers of AFP and β -HCG were examined in all patients. Highly elevated AFP was recorded in seven patients, and highly elevated β -HCG was recorded in one

| Case #. | Serum maker | | Histological marker | | | | | | |
|------------|---------------------------------|------------------------------|---------------------|------|---------|------|-----|-----|-------|
| | AFP ^{&} (ng/ml) | HCG [∆] (mIU/mI) | СК | CD30 | OCT-3/4 | PLAP | AFP | HCG | MIB-1 |
| 1 | + | - | + | + | - | - | - | - | 40 |
| 2 | + | - | + | + | + | + | + | + | 60 |
| 3 | + | - | + | + | +/- | - | - | - | 50 |
| 4 | - | - | +/- | + | + | - | + | - | 70 |
| 5 | + | - | + | - | + | - | + | - | 50 |
| 6 | + | + | + | + | + | + | + | + | 90 |
| 7 | + | - | + | + | - | +/- | +/- | - | 40 |
| 8 | - | - | + | +/- | +/- | - | +/- | +/- | 70 |
| 9 | - | - | + | - | + | +/- | +/- | - | 40 |
| 10 | + | - | - | + | + | - | + | - | 70 |

Table 1. Summary of serum markers and immunohistochemistry features of intracranial embryonal carcinoma

Abbreviations: AFP: alpha fetoprotein; HCG: human chorionic gonadotropin; MIB-1: Management Information Base-1; OCT-3/4: octamer binding factor 3/4; PLAP: placental alkaline phosphatase. AFP[&]: AFP (+): \geq 12 ng/ml; AFP (-): <12 ng/ml; HCG^{Δ}: HCG (+): \geq 5 mIU/ml; HCG (-): <5 mIU/ml.

patient. The number of patients with elevated serum tumor markers and the ranges of tumor markers by histology are summarized in **Table 1**.

Histology and immunohistochemistry

The embryonal carcinoma was composed of large cells that proliferate in cohesive nests and sheets, form abortive papillae or line irregular, gland-like spaces. Tumor cells might exceptionally replicate the structure of the early embryo, forming "embryoid bodies" replete with germ discs and miniature amniotic cavities. Markedly enlarged nucleoli, abundant clear to somewhat violet-hued cytoplasm, a high mitotic rate and zones of coagulative necrosis completed the histological picture. The constituent cells uniformly showed dense and diffuse cytoplasmic labeling for cytokeratins, attesting to their differentiation along epithelial lines and distinguishing these neoplasms from most germinomas (with which they shared PLAP and OCT-3/4 immunoreactivity). In addition, the tumor cells have a relatively high MIB-1 labeling index ranging from 40% to 90%. All the immunohistochemical results referred to Figures 2, 3 and Table 1.

Survival analysis

All the patients had received follow-up with a median follow-up period of 23.5 months (range 10 to 48 months). All the ten patients had

recurrence and died from the ECs. The median overall survival was 23 months (standard error =3.16 months, 95% confidence interval (CI) =17-29 months). The median OS time for EC with TR compared to STR was 35 months (95% CI 21-49%) to 20 months (95% CI 15-25%) (P=0.028). TR was demonstrated to be significantly associated with OS. The median OS time for patients with normal AFP compared to elevated AFP was 28 months (95% CI 20-36%) to 20 months (95% CI 15-25%) (P=0.49). Since elevated B-HCG was found only in one case, it was difficult to have a statistical com-

parison. Though patients with elevated AFP seemed to have a poorer survival, these differences did not reach statistical significance. Details of the survival analysis results are summarized in **Figure 4**.

Discussion

EC is an uncommon subtype of intracranial GCTs. Due to the rarity, most of ECs are described as isolated case reports in the literature. The clinical aspects, neuroimaging features, treatment protocol and prognosis of ECs are still obscure. The clinical aspects and therapeutics choice also refer to the general intracranial GCTs. It is necessary to seek the own characteristics of the rare neoplasm. Intracranial GCTs are more common in children and in young adults [10-12], and show a male bias [9, 11, 13]. The majorities of GCTs arise in the pineal or suprasellar regions [11, 14, 15], partly develop at multiple sites [14]. The basal ganglia and cerebellum are also common tumor locations [11]. However, male: female ratio varies with tumor location and histology. Mature teratoma shows a female predominance (ratio 0.6:1), while immature teratoma has no sex bias [11]. It is also reported GCTs in the pineal region and basal ganglia affect predominantly males, while neurohypophyseal GCTs have a slight female preponderance [2, 12]. In our series, EC has a median age of 12.5 years upon initial diagnosis and has a male to female rate



Figure 2. Photomicrographs of Case 2 under high magnification (× 400). Microscopically, H&E stain shows that this tumor is composed of large cells that proliferate in cohesive nests and sheets, form abortive papillae or line irregular, gland-like spaces. (A) Immunohistochemical stain shows that the tumor cells are positive for AFP (B), β -HCG (C), PLAP (D), and CK (E). The tumor cells have a relatively high MIB-1 labeling index (60%) (F).



Figure 3. Photomicrographs of Case 6 under high magnification (× 400). Microscopically, H&E stain shows that this tumor is composed of large cells that proliferate in cohesive nests, pile up together, and have undefined boundary; the cells are large and have polygonal appearance; the nuclei are irregular and vesicular, the nuclear membranes are clear, and the nucleoli are prominent (A). Immunohistochemical stain shows that the tumor cells are diffusely positive for CK (B), the tumor cell membrane are strongly positive expression for CD30 (C), and the tumor cell nucleus are strongly positive expression for OCT-3/4 (D).

of nine to one. The bias of hormone levels might conduce to the sex difference in EC.

The clinical signs and symptoms of the different histological subtypes are not specific [2].



Figure 4. A: Kaplan-Meier overall survival (OS) estimates of EC patients who underwent total resection (solid line) versus patients with subtotal resection (dotted line). The median OS time for patients with total resection compared to subtotal resection was 35 months (95% confidence interval 21-49%) and 20 months (95% confidence interval 15-25%) (*P*=0.028). B: Kaplan-Meier OS estimate of EC patients who had normal AFP (solid line) versus patients with elevated AFP (dotted line). The median OS time for patients with normal AFP compared to elevated AFP was 28 months (95% confidence interval 20-36%) and 20 months (95% confidence interval 15-25%) (*P*=0.49).

The clinical features of intracranial GCTs are related to the tumors' locations and sizes. Ocular signs and obstructive hydrocephalus are usually the common initial signs. The majority of patients of the pineal region present with symptoms of intracranial hypertension, diplopia and Parinaud's syndrome as a result of obstruction of the aquaduct, invasion of the tectal plate, and hydrocephalus [15]. The patients of suprasellar tumors present with diabetes insipidus, amenorrhea and visual disturbance because of the compression or invasion of the optic chiasm [2]. Pineal GCTs usually present with signs of increased intracranial pressure resulting from obstructive hydrocephalus, often requiring shunt placement or ventriculostomy. In the present study, the patients with pineal ECs underwent either ventriculoperitoneal shunt (n=2) or endoscopic third ventriculostomy (n=2) in order to relieve the obstructive hydrocephalus.

The special features of GCTs in CT and MRI scans are rare. On plain CT scan, GCTs are slightly high- or high-density masses, and the tumors are homogeneous in density and homogeneously well enhanced after contrast enhancement. On MRI, most of the tumors are isointense or hypointense on T1-weighted imaging and isointense to hyperintense on T2-weighted imaging, the tumors show strongly

heterogeneous or homogeneous enhancement after contrast enhancement [7]. In the present study, all the tumors are isointense or hypointense on T1-weighted imaging and isointense or hyperintense on T2-weighted imaging. The tumors show strongly heterogeneous or homogeneous enhancement after administration of gadolinium. The results were similar to the previous reports [16]. It is difficult for us to find an affirmative neuroimaging marker to distinguish EC from other subtypes of GCTs only by the CT and MRI data. However, combining the MRI results with the clinical data, such as age, gender, initial symptom, location and serology markers, EC might be diagnosed before the operation. Liang et al. reported not only the diagnosis of GCTs but also the prediction of the subtype might be assessed by combining imaging features with the age, sex, symptoms and signs [16]. It is also supported that, to some extent, MRI enable distinction among four common solid diseases in the pineal gland: germinoma, teratoma, pineoblastoma, and glioma [17, 18].

Tumor markers play an important role in the diagnosis of intracranial GCTs. The most common markers are AFP and β -HCG, although PLAP and the soluble isoform of c-Kit may become clinically relevant in the future [19, 20]. AFP and β -HCG can be observed in the serum

and cerebrospinal fluid, which are not secreted by other primary tumors in the brain. Any detectable elevation of AFP may be considered for the diagnosis of non-germinomatous GCTs without the histological confirmation [21]. The levels of tumor markers are associated with prognosis, and the patients with elevated AFP appear to have poorer survival [11, 22]. Lee et al. found that the intracranial GCT patients with elevated AFP or β-HCG had a poorer survival with borderline significance (P=0.0568) [11]. In the study of Kim et al., the GCT patients with elevated AFP and β-HCG appeared to have a poorer survival (P=0.08), though these differences do not reach statistical significance [22]. In our series, the median OS time for patients with normal markers compared to elevated AFP was 28 months to 20 months (P=0.49). Patients with elevated AFP seem to have a poorer survival, while these differences do not reach statistical significance. More data should be collected in order to evaluate the role of the AFP in diagnosing the EC and predicting the prognosis.

Excellent results have been obtained for mature teratoma with curative surgery, and for pure germinoma with effective radiation therapy. However, the remaining tumor types are refractory to conventional treatment with surgery and irradiation. Matsutani et al. analyzed 153 cases of GCTs and classified them into good, intermediate, and poor prognosis groups. The 10-year survival rates of patients with pure germinoma, mature teratoma and malignant teratoma were 92.7%, 92.9% and 70.7%, respectively. However, the patients with pure malignant GCTs (EC, yolk sac tumor, and choriocarcinoma) had a 3-year survival rate of 27.3% [2]. Most patients with nongerminomatous tumors did not survive beyond 3 years [9, 23]. In the present study, the median survival time of intracranial EC is 23.5 months, and shows a poor prognosis.

The treatment of malignant non-germinomatous GCTs follows a multi-model concept that includes tumor resection for local tumor control, radiation to cover leptomeningeal tumor spread, and chemotherapy to eliminate systemic tumor dissemination [24, 25]. The extent of the resection is generally regarded as one of the most important prognostic factors in many tumors. For non-germinomatous GCTs, the survival rate was significantly associated with extent of tumor resection [5, 26, 27]. In the

present study, the median survival time for EC with TR compared to STR was 35 months to 20 months. TR is significantly related to OS (P=0.028) and had a better prognosis, which might be a vital index to evaluate the prognosis of EC. However, several factors could prevent TR, such as the location, size, blood loss, adhesions, and the pathological subtypes (causing severe adhesion). The relative roles of surgical resection, radiotherapy, and chemotherapy in the management of patients with such lesions have remained controversial [28]. There is currently no consensus on the best treatment protocol for EC. In Europe and North America, delayed surgery for persistent disease after chemotherapy is preferred [29], while in Japan, more aggressive resection is advocated for therapeutic and prognostic implications [2, 30]. Postoperative radiotherapy and chemotherapy might play a vital role in preventing recurrence following subtotal resection. More data are required to assess the role of radiotherapy and chemotherapy in EC treatment in the future.

There are some limitations of this study. First, the data for our study were collected retrospectively; therefore, potential bias might exist. Second, the initial operations for several cases were performed in two hospitals, and some patients' subsequent radiation and chemotherapy treatment were conducted at different hospitals. The treatment dose and protocol might have different choice. Third, the patients' conditions were obtained by clinical services and telephone interviews, and some patients had no neuroimaging data with which to assess the recurrences time for evaluations. Moreover, the small cohort in this study might not be well suited to an assessment of our treatment policy. The gold standard for evaluating our treatment policy would be a prospective randomized trial, but this approach is not possible due to the rarity of EC.

In conclusion, EC is a rare subtype of intracranial germ cell tumors with a tendency to present in younger patients and has a male bias. EC has a poor prognosis. The extent of resection is an important prognosis factor. More data should be collected in order to evaluate the role of the AFP in diagnosing the EC and predicting the prognosis.

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Disclosure of conflict of interest

None.

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