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Original Article

Primary intracranial choriocarcinoma: a report of 8 cases with review of literature

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Abstract: Objective: Primary intracranial choriocarcinoma is a rare intracranial neoplasm. We discuss its clinical features and treatment in a pediatric population. Methods: We retrospectively studied choriocarcinoma cases in our center from May 2002 to January 2015. Eight patients were diagnosed with primary intracranial choriocarcinoma and included. Pre- and post-operative CT and MRI were examined and blood serum and cerebrospinal fluid (CSF) were sampled to measure alpha-fetoprotein (AFP), carcinoembryogenic antigen (CEA), and human chorionic gonadotrophin (HCG). Results: All patients were male, aged between 5-17 years, (mean 11 years). The major presenting symptoms were headache, and dizziness with vomiting. All patients presented with hydrocephalus. The duration of onset was 10 days to 3 months; five patients had eye movement disorder and diplopia. Two patients had precocious puberty; and one patient had diabetes insipidus. HCG was elevated in all patients (serum level ranged from 1190-12000 IU/L CSF level ranged from 990-4651.56 IU/L). Three patients received preoperative radiotherapy. Eight patients received ventriculo-peritoneal shunts immediately after admission. Seven patients underwent surgery the remaining patient received chemotherapy with radiotherapy. Seven patients received postoperative chemotherapy. Hemorrhage and tumor growth occurred in patients who underwent preoperative radiotherapy. Follow-up was from 1 to 60 months; three patients died during follow-up and four survived. The mean survival time was 23.6 months. Conclusions: Extremely elevated HCG levels in serum and CSF may help diagnosis of primary intracranial choriocarcinoma. Based on these cases, we are concerned that preoperative radiotherapy may increase the hemorrhage occurrence. Surgery combined with chemotherapy may be a more effective treatment.

Keywords: Intracranial, primary choriocarcinoma, germ cell tumor, treatment

Introduction

Germ cell tumors (GCTs) comprise 3% to 11% of all intracranial neoplasms in children and 1% of all primary intracranial neoplasms in adults [1, 2]. Primary intracranial choriocarcinoma (PICCC) is the most malignant type of primary intracranial GCT; the incidence of PICCC is very rare; generally, it accounts for 3%-5% of all intracranial GCTs. However, higher incidence of PICCC has been reported in Asia, especially in Japan. The Committee of Brain Tumor Registry of Japan reported the incidence was 3.2% of all primary intracranial GCTs [3-6]; PICCCs are mostly found in the pineal and suprasellar regions, less frequently in the parasellar region and lateral ventricle, and some PICCCs may metastasize to the lungs [7-11].

PICCC is characterized by extraembryonic differentiation along the trophoblastic lines, and involves high serum and cerebrospinal fluid (CSF) levels of human chorionic gonadotrophin (HCG) [12-14]. As HCG level is extremely elevated in patients with choriocarcinoma this is an important characteristic for diagnosis of PICCC [1, 2, 15-20]. The production of HCG can cause precocious puberty, a specific symptom of PICCC occurring in males [14, 21, 22]. Other symptoms are caused by neurologic effects that are caused by obstructive hydrocephalus and involvement of ocular pathways [13]. The major symptoms include headache, nausea and vomiting, lethargy, and diplopia [13]. Alpha-fetoprotein (AFP) may also support the diagnosis although it is not as obvious as HCG levels [2, 16]. CSF cytological examination and bone marrow examination may also help to indicate spinal cord metastasis or systemic spread [4]. The prognosis of PICCC is very poor due to its high malignancy, but the combination of surgery with radiotherapy and chemotherapy has increased the overall survival rates of chorio-

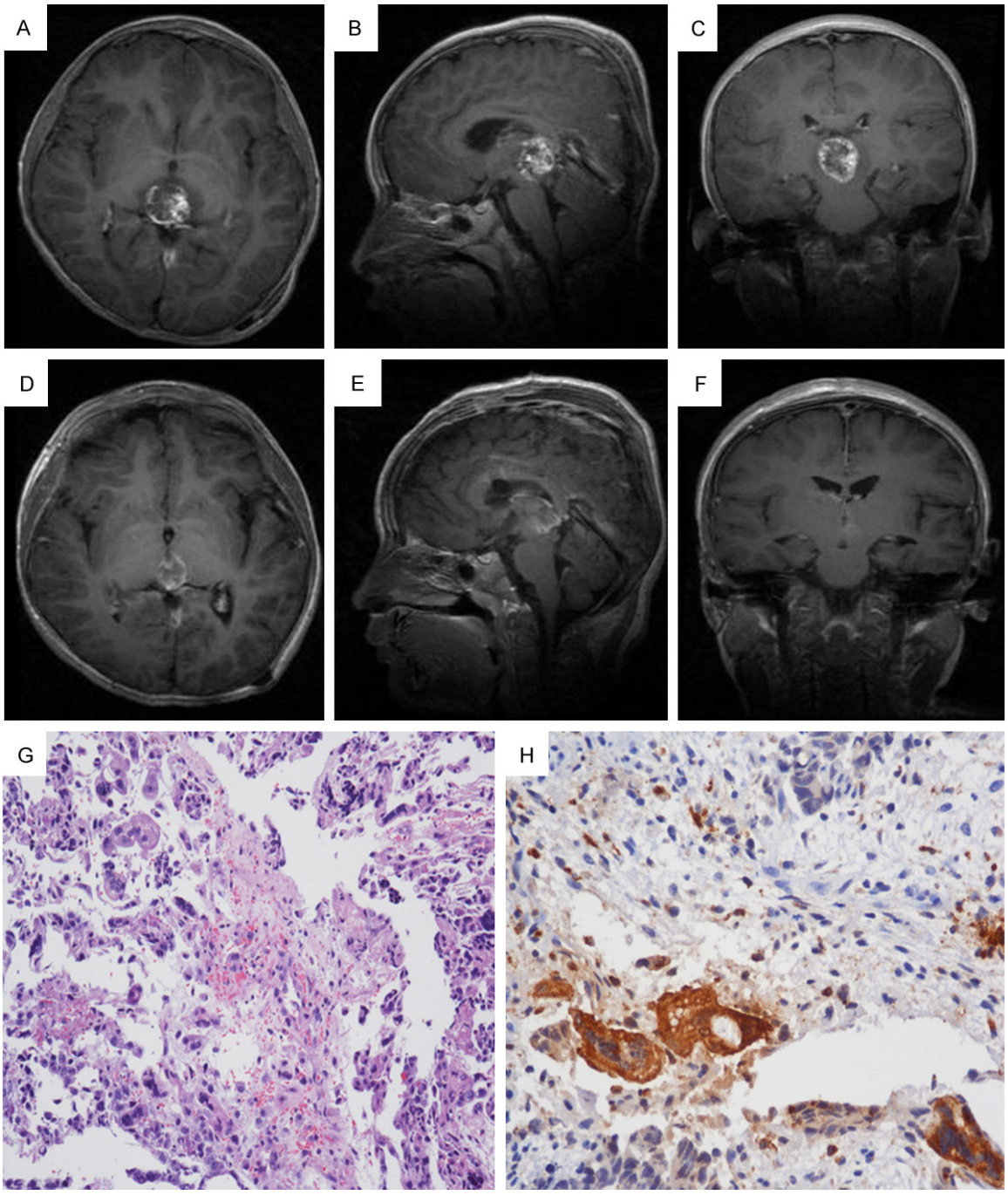

Figure 1. The 5-year-old male patient received surgery, and magnetic resonance imaging (MRI) showed that the lesions had been completely removed. The pathology results confirmed intracranial choriocarcinoma. MRI images: A-C: Tumor located at pineal area; MRI scans showed heterogeneous contrast enhancement. D-F: Postoperative MRI scans showed total removal of the mass lesion. G: HE staining showed typical synctytiotrophoblastic and cytotrophoblastic cells. Microscopically, there were hemorrhage and necrosis tissue in the tumor specimen. H: Immunohistochemical staining showed positive HCG marker.

carcinoma patients in recent years [12-14, 23, 24].

In order to provide more information on the clinical features and treatment of this rare condition we present 8 cases of choriocarcinoma in our center. The clinical findings, radiologic findings, surgical treatment and outcomes were summarized to diagnose and consider the treatment modalities for these rare lesions.

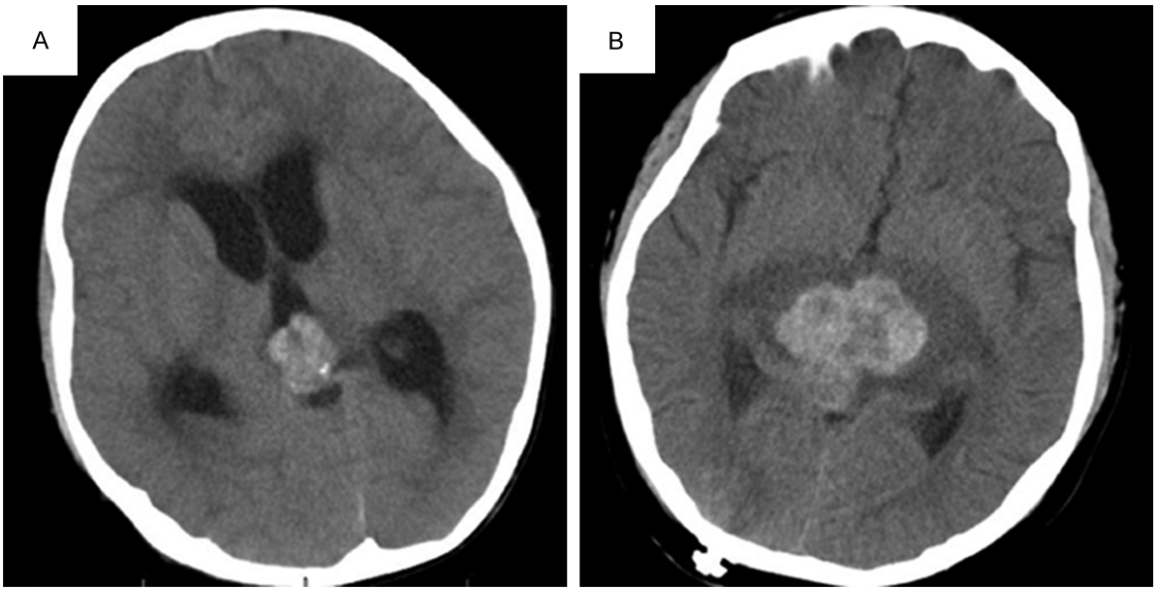

Figure 2. A 17-year-old male patient. A: The tumor showed iso- to slight hyper-density on CT scan, with calcification. B: The tumor enlarged, accompanied with intratumoral hemorrhage and edema on surrounding tissue, 3 days after pre-operative radiotherapy.

Materials and methods

Patients' population and symptoms

We report on our retrospective analysis of choriocarcinoma patients treated in the Beijing Tiantan Hospital from May 2002 to January 2015. The inclusion criteria were as follows: 1. under the age of 18 years, 2. pathologically confirmed as primary intracranial choriocarcinoma, or clinically diagnosed with primary intracranial choriocarcinoma according to specific tumor markers (serum and CSF HCG levels extremely elevated) and typical findings on magnetic resonance imaging (MRI).

The patients were excluded if he/she had a primary tumor in testes or other locations and intracranial cases.

The study was approved by the hospital's Ethics Committee. The patients and their guardians signed informed consent.

Neuroradiological evaluation

Computed tomography (CT) and MRI examinations were performed in the week before the surgery. MRI was performed again one week after the surgery and at 1, 3, and 6 months after surgery. For patients in a stable condition after surgery, MRI examination and follow-up were conducted every 6 months.

Auxiliary examination

Preoperative blood serum and CSF were taken from all patients to examine the tumor markers; alpha-fetoprotein (AFP) and carcino-embryogenic antigen (CEA) and HCG. HCG was also tested one week after surgery and one week and two weeks after starting chemotherapy, which was started one month after surgery, HCG was then tested every month.

Treatment strategies

Some patients received treatment before admission to our hospital: 3 patients were misdiagnosed with germinoma before surgical confirmation, and received radiotherapy (2.0 Gy/time, 5 times in total). All these 3 patients suffered exacerbations in the week after radiotherapy. And CT re-examination found an increase in tumor size or bleeding. Another patient received stereotactic radiotherapy in another hospital, this exacerbated the condition and he had a tumor hemorrhage too, and was then transferred to our hospital. Four patients received preoperative chemotherapy and their HCG level was sustained or declined with treatment, but was elevated several months later.

All eight cases underwent ventriculo-peritoneal (V-P) shunt immediately after admission to our hospital. After their intracranial hypertension

Table 1. Summary of clinical data in 8 patients with PICCC

No	Age	Pre-Op Radio	Pre-Op Chemo	Tumor characteristics	Blood HCG (IU/L)			Degree of resection	Adjunctive therapy	Survival time (months)	Death	Tumor Recurrence
Received op					Pre-op	Post-op	Post-chemo					
1	10	Y	N	Hemorrhage	2942.73	1346.61		Total	N	1	Y	Y
2	17	Y	N	Hemorrhage	1276.21	582.94	114.72	Total	Chemo	>60	N	N
3	17	Y	N	Hemorrhage	2849.25	750.73	403.76	Total	Chemo	22	Y	Y
4	11	N	Y	N	1569.16	625.35	287.89	Subtotal	Chemo	13	Y	Y
5	5	N	Y	N	7100	3410	270.9	Total	Chemo	>45	N	N
6	7	N	Y	N	1190	969	221	Total	Chemo	>18	N	N
7	9	Y	Y	Hemorrhage	2915	122.7	5.41	Subtotal	Chemo+radio	6	N	Y
Not op					Pre-chemo		Post-chemo					
8	12			Disseminating	12000		1.2		Chemo+radio	>19	N	N

Abbreviations: PICCC = primary intracranial choriocarcinoma; HCG = human chorionic gonadotrophin; CSF = cerebrospinal fluid; Op = Operation; Chemo = Chemotherapy; Radio = Radiotherapy.

was relieved (1-2 weeks after shunt), seven patients underwent surgery via the transcallosal interforniceal approach to remove the tumors, and underwent chemotherapy one month after the surgery (VMPP program: composed of vincristine, methotrexate, bleomycin, and cisplatin). The one remaining case was not suitable for surgery because the tumor had spread to the third ventricle. Therefore, the VMPP regimen was used for chemotherapy, and then radiotherapy was performed (1.6 Gy/time, 33 times in total). Finally, one more cycle of chemotherapy was performed.

Results

Patient characteristics

There were 8 patients in the cohort, all the patients were male, their ages ranged from 5-17 years, and the mean age was 11 years. The major presenting symptoms were headache, and dizziness accompanied with vomiting due to high intracranial pressure. All patients presented with hydrocephalus during admission. The duration of onset was 10 days to 3 months; five patients had eyes movement disorder and diplopia. Two patients had precocious puberty; and one patient had diabetes insipidus. Nonspecific symptoms-such as paresis on lower extremities and hearing loss, presented in one patient. One of the patients had preoperative stereotactic radiotherapy in their local hospital; the tumor was found to have metastasized to the thyroid gland, and later re-examination of the CT scan showed tumor hemorrhage. All patients were diagnosed with primary intracranial choriocarcinoma, and it was confirmed that the tumors were not from testicular origin or any other sites.

Seven patients had tumors located in the pineal area (**Figure 1A-C**), one patient had a tumor located in the sellar area that had disseminated to the third ventricle. The tumors' volume ranged from 3 to 5 cm in diameter. Post-contrast T1 weighted image showed heterogenous nodular contrast enhancement. CT revealed iso- to slight hyper-density in 8 cases, 2 of which had calcification (**Figure 2A**). Post-radiation tumor stroke occurred in 3 cases (**Table 1**).

AFP and CEA were normal in all patients. Serum HCG was significantly elevated in all patients (ranged from 1190-12000 IU/L). CSF level of HCG was also increased (ranged from 990-4651.56 IU/L) although it was not as significant as the blood serum level of HCG.

Operative findings

During surgery we found that the tumors were lobulated or oval in shape, located in the third ventricle and posterior part of the third ventricle. The tumor volume ranged from 3-5 cm in diameter; appeared to be red-grayish solid and tenacious. Plenty of abnormal vascular structures were supplying the tumor; most of the tumors were presented with intratumoral hemorrhage due to its rich vascular supply. The tumor tightly adhered with the surrounding normal tissue and veins; some of the tumors had a pseudo membrane and some had invaded the surrounding tissue. Total resection was achi eved in five patients (**Figure 1D-F**), and subtotal resection was achieved in two patients in whom the tumor tightly adhered with the surrounding normal tissue and vein.

Pathological findings

HE staining showed typical synctytiotrophoblastic cells that appeared as large, spindle-shaped, multinucleated cells; many nuclei were large, irregular and hyperchromatic, with prominent nucleoli in eosinophilic cytoplasm that contained many vacuoles. Cytotrophoblastic cells appeared to be medium-sized cells with single uniform nuclei in clear cytoplasm. Microscopically, there were hemorrhage and necrosis tissue in the tumor specimen (**Figure 1G**); immunohistochemical staining showed positive HCG marker (**Figure 1H**).

Post-operative treatment and follow-up

Six patients had post-operative chemotherapy; only one patient did not receive chemotherapy because one month after surgery the patient went into a coma rapidly due to recurrence of the tumor, and lost the opportunity for further treatment. We followed-up all patients after surgery. Three of five patients who underwent total resection were alive during follow-up; and two died due to tumor recurrence. One of two patients who underwent subtotal resection was alive during follow-up; and one died due to tumor recurrence. One patient who received chemotherapy and radiotherapy without surgical treatment was alive at the time of follow up; and the result is satisfactory-the tumor marker was reduced to normal levels, and there was a reduction of the tumor volume. Postoperative examination showed reduction of blood and CSF HCG level, and the HCG levels continuously decreased after chemotherapy (**Table 1**).

Discussion

PICCC is a highly malignant neoplasm composed of biphasic cellular components of mononuclear cytotrophoblasts and multinucleated syncytiotrophoblasts. Koyama S et al reported PICCC presents between 3 and 22 years of age (mean age 11.8 years), and Lv XF et al reported the ages of patients ranged from 7 to 19 years (mean 11.9 years). Both reported that PICCC has male predominance [5, 8]. Consistent with that, the mean age in our presented case was 11 years old and all of the patients were male.

PICCC has been reported at various sites, including the pineal region [14, 17, 24-26], suprasellar or parasellar region [10, 21, 27], with less common sites including the lateral ventricle [12, 28], basal ganglia [12, 19], septum pellucidum [8] and intraventricular-trigonal [26]. Several studies have reported CSF dissemination of PICCC at time of diagnosis [12]. In our case report, seven patients had a tumor located in the pineal area and one patient had a tumor in the sellar region that had disseminated to the third ventricle. Symptoms and signs of PICCC are varied, most of the patients have obstructive hydrocephalus, ophthalmologic signs may develop-such as impairment of upward gaze, abnormalities of the pupil, paralysis or spasm of convergence, and nystagmus retractorius. Less common symptoms include precocious puberty or delayed onset of sexual maturation. In our cases, all patients had elevation of the HCG in both blood serum and CSF; two patients presented with precocious puberty-the explanation for this symptom is that the tumors contain syncytiotrophoblastic giant cells that can produce HCG and induce luteinizing hormone, which has a role in stimulating Leydig cells in the testes to secrete testosterone [29].

HCG is a useful biologic tumor marker characteristic of choriocarcinoma. Markedly elevated serum HCG level is strongly suggestive of choriocarcinoma or mixed GCTs with choriocarcinoma elements [6]. It appears, therefore, a markedly elevated serum HCG level of >5000 very likely has choriocarcinoma components [5]. The titers of HCG and AFP reflect the number of cells secreting these proteins; this is useful for differentiating tumors with predominant choriocarcinoma. Matsutani et al [6] reported that mixed germ cell tumors with choriocarcinoma components may have elevation in blood serum level of HCG above 2000 IU/L, and for mixed germ cell tumors without choriocarcinoma components, the level of HCG is below 770 IU/L. Elevated HCG has been reported in patients with choriocarcinoma in many reports [1, 2, 15-20]. Based on our experience, significant elevation only in blood HCG of >1000IU/L is enough to diagnose PICCC, but if both HCG and AFP level are significantly elevated then the diagnosis would be towards mixed germ cell tumors. In our case, the blood serum HCG ranged from 1190 to 12000 IU/L; after chemotherapy, the reductions of HCG levels were varied. The seventh patient in our cases had their HCG level reduced almost to a normal level, but 3 months later the HCG level continuously increased-consistent with the recurrence of the

tumor; this phenomenon may suggest that reduction of the HCG level is a measure of treatment efficacy. However, reduction of HCG level cannot become a standard to predict the prognosis. Other tumor markers such AFP may help the diagnosis of PICCC; and elevation of AFP level has been reported in patients with intracranial choriocarcinoma [2, 16], although this serum level is not as accurate as HCG level in choriocarcinoma diagnosis. In our case report, no elevation of AFP level was found; and based on our experience; elevation of AFP might have a high probability of mixed germ cell tumors rather than choriocarcinoma.

PICCC may have varied responses to treatment; correct pretreatment diagnosis is important to determine the proper therapeutic plan. Imaging is important to support the diagnosis of PICCC. The CT may appear high density or isodense, with higher prevalence of pineal calcification [10, 30]. However, calcification on CT images is not a typical characteristic of PICCC; two patients in our case presented with calcification on their CT scan. MRI scans showed better resolution; with an ovoid or irregular mass with a large hemorrhagic component; the presence of hemorrhage is a characteristic feature of PICCC, and contrast gadolinium usually show marked heterogeneous enhancement [8, 12, 14, 31]. Frequent hemorrhage is seen in PICCC due to the fragility of vessels perfusing these trophoblastic tumors and the innate capacity of trophoblastic cells to invade and erode vessel walls [5, 32]. Three patients in our case series presented with intratumoral hemorrhage-these phenomena have been reported in many choriocarcinoma cases and may become a typical characteristic of this tumor. The incidence of hemorrhage is rare in germ cell tumors without a choriocarcinoma component. Extracranial choriocarcinoma, especially arising from the gonad, is known to spread via a vascular route and often metastasizes to the central nervous system in 3%-28% of patients [33]. Therefore, choriocarcinoma metastasis from the genital system is an important consideration as a differential diagnosis.

Hydrocephalus is often present in PICCC due to most of the tumor location of the pineal area which usually obstruct the Sylvian aqueduct. In our case, seven patients who had tumors in the pineal region presented with obstructive hydrocephalus and had significant high intracranial pressure. We immediately performed a V-P shunt after admission to relieve the pressure. We considered that V-P shunt had several advantages in cases of hydrocephalus secondary to obstruction of the ventricular system by the tumor. First, delay in management of hydrocephalus may result in loss of consciousness, even coma, and early management may prevent this fatal outcome. Second, we preferred to use an adjustable V-P shunt so that controlling the intracranial pressure would become more flexible, and the pressure could be adjusted according to the patient's condition. It was also important to note that rapid reduction of the intracranial pressure may cause intratumoral hemorrhage, and that is why we did not chose to use endoscopic third ventriculostomy, because the intracranial pressure is uncontrollable. Third, relieving the intracranial pressure may be of benefit during surgery, since a high intracranial pressure may increase the mortality rates and rapid drops of blood pressure may occur after opening the dura due to the sudden relief of the pressure. Fourth, a V-P shunt may avoid postoperative secondary hydrocephalus due to adhesion of the ventricular wall. Intracranial choriocarcinoma can metastasize to other organs through the blood circulatory system, seeding of the tumor is restricted to the nervous system only through CSF circulation [4, 34]. In our case, we did not find any tumor seeding in the peritoneal cavity through the V-P shunt, but more follow-up and related examinations are needed.

The results of radiation therapy in germ cell tumors were varied. Fuller et al reported that radiation alone produced a 5 year survival rates of only 30-40% for non-germinoma germ cell tumors (NGGCTs) [35]. Haas-Kogan et al reported a 5-year OS rate of only 68% for NGGCT compared with 93% for germinoma [32]. The efficacy of radiation therapy in choriocarcinoma is still in debate, because radiation therapy in NGGCT has fewer prognosis results compared with germinoma. Sung DI et al reported higher radiation dosages (5000 to 5500 rads) had reduced local recurrence rates from 47% to 10% [36]. In our case, because of insufficient knowledge of PICCC and the consideration of germinoma in the early years of diagnosis; three of the patients underwent radiotherapy, and the tumors enlarged rapidly after the treatment. Two of the patients then had an intratumoral hemorrhage; one patient had an intratumoral hemorrhage after radiotherapy at their local hospital. Based on our experience, we suggest preoperative radiotherapy can be given in NGGCT that has a slightly increased

HCG level. However, preoperative radiotherapy is not recommended when HCG is increased to more than 1000 IU/L, especially in cases with a high probability of choriocarcinoma. And because of the high risk of hemorrhage, we also think biopsy should not be suggested.

In recent years, chemotherapy for extracranial choriocarcinoma has shown good results; these achievements may provide a new hope in treating intracranial choriocarcinoma. The antitumor effects of cisplatin were first reported by Rosenberg and VanCamp in 1970s. Platinum-based multiagent chemotherapy has dramatically improved the outcome for patients with nongerminomatous germ cell tumors arising in any primary site. Other authors have recommended the use of platinum-based multiagent chemotherapy [4, 26, 28, 29].

Standardized protocols exist worldwide for the treatment of GCTs. Based on elevated serum or CSF HCG-β these tumors should be treated as NGGCTs and undergo upfront chemotherapy. Surgery is used for cases where tumor/markers persist after chemotherapy or there is marked growth during treatment. In most cases of PICCC surgery cannot be avoided because of their high malignancy that cannot be controlled by chemotherapy alone. Preoperative chemotherapy may benefit surgery; in some cases, the tumor will shrink and pseudo membrane formation may occur as a result of the pathophysiological reaction in patients who underwent preoperative chemotherapy, which may reduce the surgical difficulty and allow the surgeon to differentiate and easily separate the tumor from the normal surrounding tissue. From our experience, in cases that are likely to be PICCC and especially in giant tumors with a diameter more than 3 cm, we highly recommend preoperative chemotherapy. For a patient who has an intratumoral hemorrhage during admission, further evaluation based on patient's condition is needed before considering preoperative chemotherapy. In our case, one patient was not suitable for surgical operation; later, chemotherapy and radiotherapy were given to the patient, and patient was stable after the treatment, there was no aggravation or recurrence of the tumor during follow-up.

In the cases reported here, 7 were given surgery and total resection was achieved in five patients; gross total resection was achieved in the other two patients. A good prognosis of 60 months survival is possible for a patient who has total resection of the tumor. We regret that we did not provide any statistical analysis due to small number of cases. Still, we suggest total resection in cases where it is possible to not do too much manipulation during surgery, which can injure surrounding normal tissue and the deep venous system. There are two main reasons; the first is because PICCC has a rich vascular supply, so tumor residue may result in a secondary hemorrhage in the surgical field; the second is because total resection may reduce the required dose for chemotherapy and the tumor recurrence rate.

At present, surgery combined with postoperative chemotherapy and radiotherapy is needed for integrative treatment of PICCC [32]. Consistently, we suggest postoperative chemotherapy for PICCC, although it is still controversial because some PICCC are resistant to the standard treatment. PICCC has a very poor prognosis, the median survival time is 22 months, and the 1 and 2 year survival rates are 61.2 and 49.8%, respectively. PICCC with intra-tumoral hemorrhage has the worst prognosis [13, 14]. Matsutani et al [6] analyzed 153 primary intracranial germ cell tumors and reported that the shortest survival rates were found in patients with choriocarcinoma. These results were consistent with study by Jennings et al [4]. Our study showed that better prognosis was achieved in patients who have total resection combined with chemotherapy.

This study has some limitations. Because PICCC is not common the number of cases was small so we could not provide any statistical analysis of the data. Inclusion of multiple centers would provide more data for analysis.

In conclusion, we present a case series of eight patients diagnosed with PICCC to provide details of the clinical features and treatment of PICCC in our center. Significantly raised HCG levels in serum and CSF is essential for diagnosis of PICCC. Our experience with these patients suggests that it is important to relieve the hydrocephalus first and preoperative radiotherapy should not be recommended to those with extremely elevated HCG level because of the chance of hemorrhage. Our experience and a literature search suggest that total resection

combined with pre-and post-chemotherapy may result in the best prognosis.

Disclosure of conflict of interest

None.

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