



Case Report

# Can mixed pure hepatocellular carcinoma and germinoma arise together in the brain?

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Received May 26, 2014; accepted February 17, 2015

## Abstract

Intracranial germ-cell tumors (GCTs) represent 10–15% of all pediatric brain tumors in East Asia. There is a wide histopathological spectrum of intracranial GCTs. Germinomas and nongerminomatous GCTs are the two major classifications. It is difficult to distinguish different subtypes of intracranial GCTs based solely on imaging studies, however, some tumor markers, such as  $\alpha$ -fetoprotein or  $\beta$ -human chorionic gonadotropin, are helpful for diagnosis. In this study we present the case of a 13-year-old girl with an intracranial mixed GCT containing a hepatocellular carcinoma and germinoma without a primary liver tumor. Based on this unique pathological diagnosis, a series of treatments were applied, including surgery for gross tumor removal, adjuvant radiotherapy, and chemotherapy. Long-term follow up indicates fair disease control. Copyright © 2015 Elsevier Taiwan LLC and the Chinese Medical Association. All rights reserved.

**Keywords:** germ-cell tumor; germinoma; hepatocellular carcinoma; pediatric brain tumor; radiotherapy

## 1. Introduction

Intracranial germ-cell tumors (GCTs) represent approximately 2–4% of pediatric central nervous system neoplasms in North America and Europe, and there has been a fivefold

increase of incidences in East Asian countries such as Taiwan and Japan.<sup>1,2</sup> GCTs have been categorized into two groups, namely, germinomas (60–70% of intracranial GCTs) and nongerminomatous GCTs (NGGCTs), based on histologic characteristics and the degrees of differentiation.<sup>1</sup> Clinical presentation of intracranial GCTs is often based on the location and size of the tumor. There are three sites in which intracranial GCTs commonly arise: the pineal, suprasellar, and basal ganglia regions.<sup>1</sup> In addition, intracranial GCTs can be classified as having good, moderate, or poor prognosis, according to Matsutani et al.<sup>3</sup> Pure germinomas have the best

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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prognosis because they are highly sensitive to radiotherapy (R/T). NGGCTs, however, are reported to have a poorer prognosis than germinoma, even after standard treatment involving combined chemotherapy (C/T) and R/T. Herein, we describe a very rare case of a mixed GCT, composed of hepatocellular carcinoma (HCC) and germinoma, which has never been reported before.

## 2. Case Report

### 2.1. History and examination

A 13-year-old girl presented with congenital hypothyroidism but was euthyroid due to regular thyroxine therapy. Her symptoms began 1 month prior to her admission in May 2006 and included nausea, vomiting, and headaches. A diagnosis of gastroenteritis had been made at another hospital, although her symptoms persisted despite the respective treatment. During that same period, she experienced a total weight loss of 4.5 kg, and a 7000-mL increase in daily urine production was also noted in the following days. On the day before her admission, the patient lost consciousness several times; each episode lasted for 1 hour. She was brought to our emergency department in June 2006. Following admission, magnetic resonance imaging (MRI) of her brain revealed an extensive mixed-solid and cystic tumor extending from the left basal ganglia to the bilateral anterior horns of the lateral ventricles, measuring approximately 65 mm in maximum diameter (Fig. 1). There was no evidence of seeding in other sites in the brain or spinal column. The patient's serum levels of  $\alpha$ -fetoprotein (AFP) were markedly elevated to 20,095 ng/mL, whereas her  $\beta$ -human chorionic gonadotropin levels were within a normal range ( $<10$  mIU/mL). Her antihepatitis B antibody was reactive, and hepatitis B virus surface antigen as well as anti-hepatitis C virus tests were all negative. Her liver biochemical measurements, including liver transaminases, aspartate transaminase and alanine transaminase, and alkaline phosphatase levels were all within normal limits.

### 2.2. Operation and pathology

Because of obstructive hydrocephalus and increased intracranial pressure, the patient underwent emergency surgery on June 14, 2006. After craniotomy, the tumor was removed piece by piece by a transcortical approach and near total tumor removal was achieved. The pathology seemed to be a mixed GCT, which included germinoma as well as HCC without other components such as squamous epithelium, respiratory epithelium, other teratomatous tissue, embryonal carcinoma, choriocarcinoma, or yolk sac tumors (YSTs). The gross pathology view of the tumor could not be obtained due to the fragmented specimen provided. Microscopically, the germinoma tumor cells had large, centrally located nuclei, prominent large eosinophilic nucleoli, as well as clear cytoplasm (Fig. 2A). Lymphocytic infiltration was noted within the tumor. Placental alkaline phosphatase (PLAP; Fig. 2B) immunoreactivity was seen in the germinoma tumor cells. The

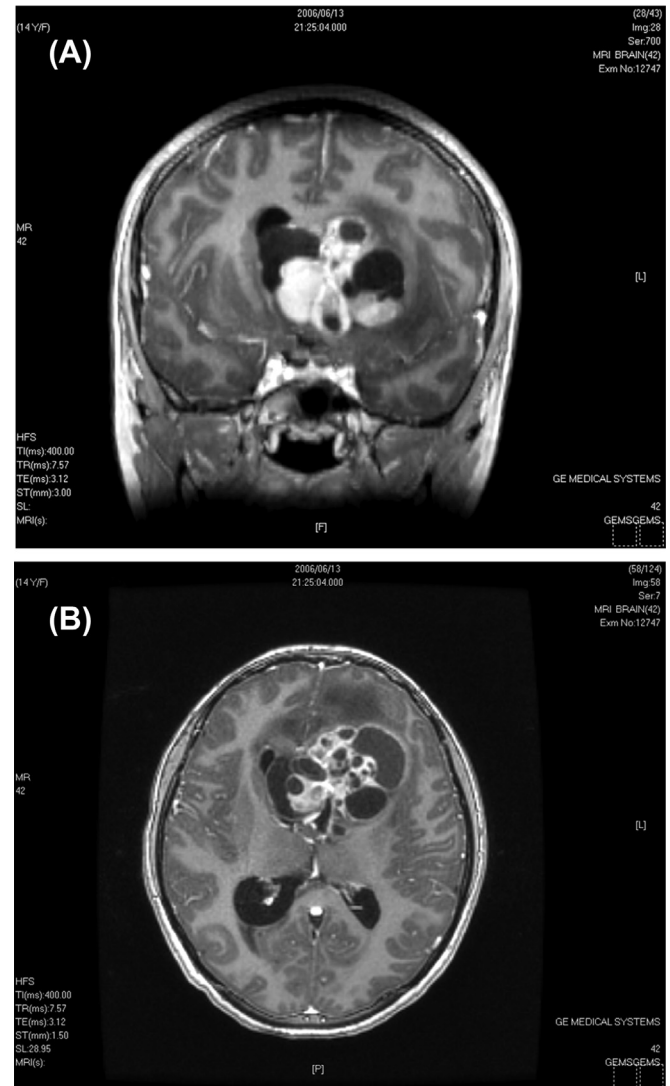


Fig. 1. T1-weighted brain magnetic resonance imaging with contrast in (A) coronal and (B) axial planes: a mixed cystic and solid tumor over the basal ganglia with extension to bilateral lateral ventricles.

other tumor component showed tumor cells arranged in sinusoidal or trabecular patterns. The tumor cells were polygonal, having a distinct cell border with a moderate amount of eosinophilic granular cytoplasm. The nuclei were round to ovoid, with discernible nucleoli (Fig. 2C). The tumor cells were immunoreactive for cytokeratin, hepatocyte-specific antigen (Fig. 2D), and AFP (Fig. 2E), but negative for PLAP. However, an abdominal computed tomography scan and sonography did not reveal any evidence of a primary liver tumor lesion. Most importantly, despite our pathologists' suggestion that it was most likely derived from a teratoma, there was no other teratoma component noted in the pathological examination.

### 2.3. Post-operative course and follow-up

Adjuvant R/T and C/T were arranged. Adjuvant R/T was planned with curative intent, and a tumor dose of 54 Gy was

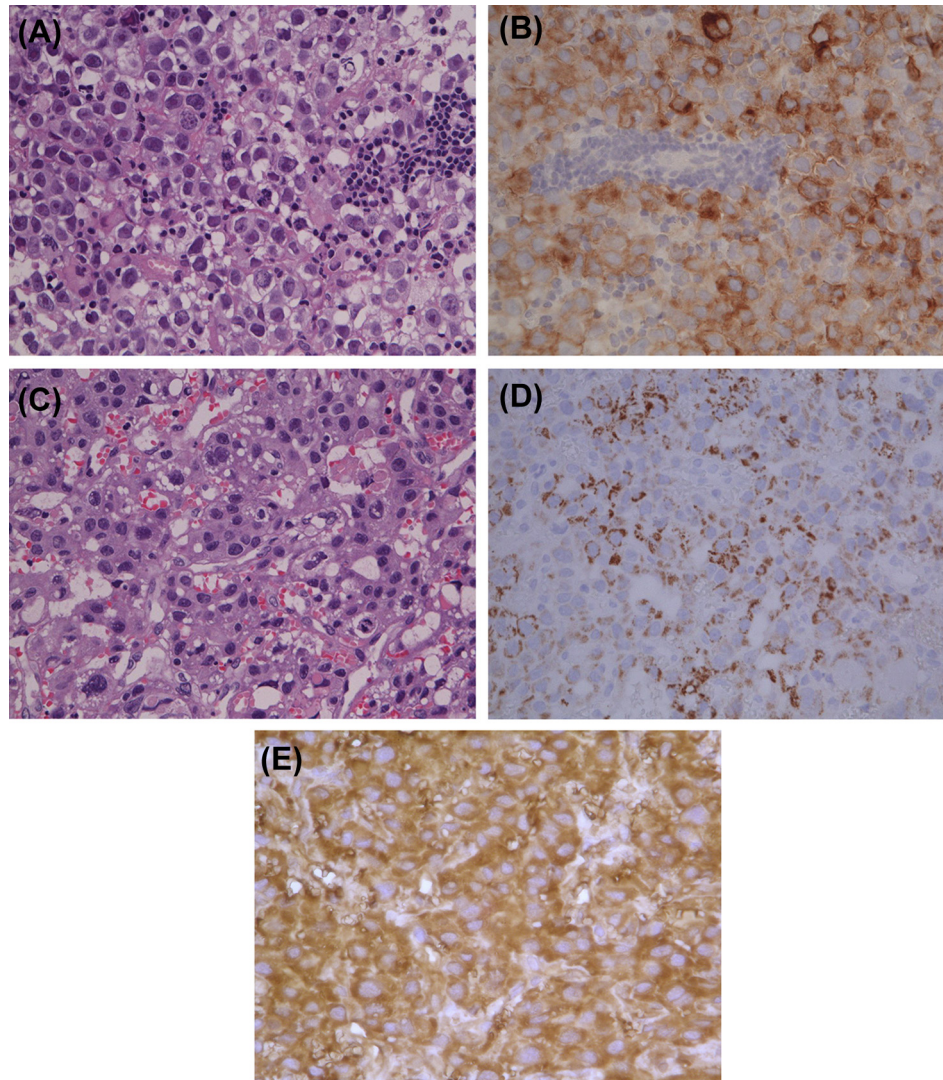


Fig. 2. (A) Germinoma tumor component [hematoxylin and eosin (H&E) stain, 400 $\times$ ]. (B) Immunoreaction for placental alkaline phosphatase (PLAP) in germinoma tumor cells (anti-PLAP, 400 $\times$ ). (C) Hepatocellular carcinoma component (H&E stain, 400 $\times$ ). (D) Immunoreaction for hepatocyte-specific antigen in hepatocellular carcinoma (hepatocyte-specific antigen, 400 $\times$ ). (E) Immuno-reaction for AFP in hepatocellular carcinoma (AFP, 400 $\times$ ).

administered to the primary tumor bed using a three-dimensional conformal technique in 27 fractions. Decreased serum levels of AFP (349 ng/mL) were noted after the R/T. Subsequent C/T, involving a regimen of vinblastine, bleomycin, etoposide (VP-16), and cisplatin (VBEP),<sup>4</sup> was administered on a monthly basis for 11 months. Symptoms of increased intracranial pressure gradually improved, and follow-up serum levels of AFP were within a normal range (<20 ng/mL) following the third course of C/T. Medications for congenital hypothyroidism and diabetes insipidus were regularly administered to the patient after she was admitted. She experienced generalized tonic-clonic seizures several times following the surgery, which were controlled with valproic acid. There was no residual tumor in the follow-up brain image. The most recent brain MRI, taken on March 16, 2011, showed typical post-operative changes and tissue loss in the left frontal region 5 years after the surgery (Figs. 3A and 3B). Although the disease was in complete remission,

complications such as panhypopituitarism, epilepsy, adjustment disorder, major depression, developmental retardation, and mild mental retardation were noted. Specifically, there was a significant decline in neurocognitive function. The patient was evaluated using the Wechsler Intelligence Scale for Children both before the diagnosis and 4 years after the surgery; the Full Scale IQ scores were 106 and 69, respectively. She has been receiving long-term occupational therapy and physical therapy since all clinical treatments were completed.

### 3. Discussion

Compared with Western countries, there is a high incidence of intracranial GCTs in Asian countries. In a single medical center in Taiwan, Wong et al<sup>5</sup> reported that intracranial GCTs comprise 14% of all primary pediatric brain tumors. The subtypes of intracranial GCTs, however, vary in histology. The World Health Organization classifies intracranial GCTs as

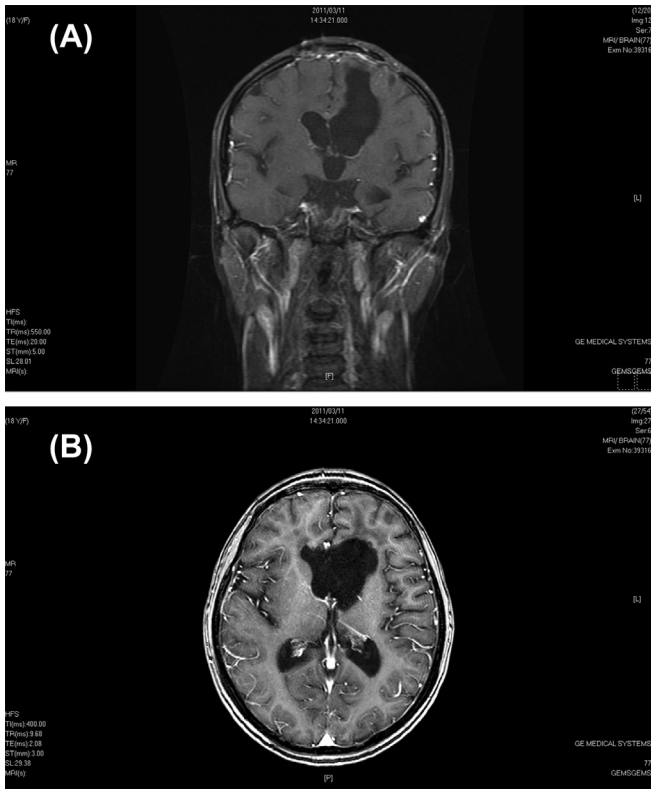


Fig. 3. T1-weighted brain magnetic resonance imaging with contrast in (A) coronal and (B) axial planes: 5 years' follow up, status after the surgery, irradiation therapy, and chemotherapy.

either germinomas or NGGCTs. NGGCTs include teratoma (mature, immature, and malignant transformations), embryonal carcinoma, choriocarcinoma, YST, and mixed GCT. In this paper, we present a very rare case of mixed GCT containing both germinoma and HCC cells in the brain. Teilum<sup>6</sup> presumed that extragonadal GCTs are derived from germ-cell progenitors that have migrated abnormally during embryonic development and have given rise to extragonadal GCTs. However, one of the possible origins of HCC might be from monodermal teratomas, which are predominantly composed of one tissue type and are most commonly seen in the ovaries. Ovarian monodermal teratomas include three main types, namely, struma ovarii, ovarian carcinoid tumors, and tumors with neural differentiation.<sup>2,7</sup> Other than monodermal teratoma, hepatoid YST was considered another explanation in this case. There are several histological variants of YSTs, one of which is hepatoid differentiation. According to Roth and Talerman,<sup>8</sup> there must be >50% component of YST for the diagnosis of variant YST to be tenable. Although both HCC and YST have a positive response to AFP stain, throughout the whole pathology findings, no YST morphological component was noted in our case. Besides, intracranial YST possesses the potential for neuraxis dissemination and very poor survival, with a median interval of approximately 1 year even after multidisciplinary treatments. However, our patient has had long-term survival for >5 years. Hence, the diagnosis of YST with hepatoid differentiation is less likely.

Germinomas are highly sensitive to R/T. Although there is not yet a uniform protocol for irradiation doses and volumes, lower doses and limited volumes (avoiding craniospinal irradiation) with or without systemic C/T are the currently accepted standards for nondisseminated diseases. Yen et al<sup>9</sup> reported that low-dose R/T without C/T is satisfactory for patients who do not have risk factors. Our patient had mixed GCT without spinal seeding, and we treated her with a standard dose (54 Gy) to a limited field of 1.5 cm surrounding the tumor bed, rather than using extended fields such as craniospinal irradiation. Adjuvant C/T was also given in combination with VBEP,<sup>4</sup> which is the standard C/T regimen for GCTs in our hospital, given its acceptable efficacy and toxicity. The long-term follow up showed a complete remission without seeding or recurrence for >5 years. Aside from the positive response to R/T seen in germinomas, HCC is also known to have good sensitivity to R/T and is thus treated with proportionate doses. Higher R/T doses result in better median survival rates. Dawson et al<sup>10</sup> reported a median survival of >16.4 months in HCC patients who received R/T doses of 70 Gy.<sup>11</sup> However, R/T is not regularly used in primary HCC due to low tolerance of normal liver tissue to irradiation, as well as nearby organs such as the intestines. Eliminating these problems, HCC in the brain is believed to respond well to R/T. However, there were several critical organs located near the tumor mentioned in this case, including the pituitary gland, the optic chiasm, and vessels in the circle of Willis. Hence, we could not administer the maximum R/T dose described by Dawson et al's study.<sup>10</sup> To balance the treatment response and R/T-related complications, a tumor dose of 54 Gy was delivered.

In conclusion, this is the first report about primary HCC arising from the central nervous system. However, the real origin remains in question. Although there were no typical pathology findings, both monodermal teratoma and hepatoid YST might be possible explanations. Our patient has achieved satisfying disease control after the combined treatment of surgery, C/T, and R/T.

## Acknowledgments

The authors are grateful for the financial support received for this study via a grant from Taipei Veterans General Hospital (Grant No. V102B-008), and the Charity Foundation of JUT Land Development Group, Taiwan.

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