Surgical Debulking Plus Adjuvant Chemoradiotherapy of a Huge Basal Ganglion Nongerminomatous Germ Cell Tumor with Long Term Survival

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Abstract: Primary central nerve system germ cell tumors are an uncommon tumor and in most cases occure in the childhood. Histologically, they can be divided to germinomas and nongerminomatous germ cell tumors (NGGCTs). The basal ganglion is an unusual location of NGGCTs and may cause the sign of increased intracranial pressure, mental deterioration, and hemiparesis. The brain MRI is the most preferred diagnostic equipment, and the serum or CSF tumor markers provide more hints to differentiate the subtypes of the NGGCTs preoperatively. Unlike germinomas which are radiation sensitive, the treatment of NGGCTs may need a combined therapy, including surgical debulking, whole brain radiation therapy and systemic chemotherapy. Although the optimal management of intracranial NGGCTs is not established, we provide a case of basal ganglion mixed germ cell tumor (Primary yolk sac tumor with germinoma component) who received near total surgical resection and adjuvant chemoradiotherapy with long term survival. To reach the maximal surgical debulking and avoid the damage of eloquent areas may be the aim of the treatment of NGGCTs for pediatric neurosurgeons and the key to prolonging the patient's survival.

Keyword: Chemoradiotherapy, Germ cell tumor, Nongerminomatous, Survival, Surgery.

INTRODUCTION

Germ cell tumors (GCTs) are classified as extragonadal if there is no evidence of a primary tumor in either the testes or ovaries. Histological, extragonadal GCTs include germinomas, and nongerminomatous GCTs (NGGCTs), like yolk sac tumors, a rare histological subtype. The central nervous system (CNS) NGGCTs usually develop in the pineal and suprasellar regions. However, some CNS NGGCTs develop in the unusual locations of the brain, such as basal ganglia and thalamus [1]. Unlike germinomas which are sensitive to the radiotherapy, NGGCTs are relatively resistant to both radiotherapy and chemotherapy. So, the outcome is substantially less favorable with long term survival rates of less than 40% [2]. The role of surgical debulking and adjuvant chemotherapy plus radiotherapy is still controversial. Hence, we report a case of mixed type NGGCTs (Primary yolk sac tumor with germinoma component) found in the basal ganglion with long term survival, which was treated by near total surgical resection and adjuvant chemotherapy and radiotherapy.

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CASE REPORT

This patient is a 12-year-old boy without any congenital disease or development disorder before. He suffered from gradual onset of left side weakness and frequently fell down from April, 2008. Initially, he was brought to neurology outpatient department for help and peripheral neuropathy was diagnosed by NCV examination. Then, he was transferred to rehabilitation clinic for rehabilitation. Because the symptom did not improve, the brain MRI was done and a large brain tumor, about 5 cm in diameter was found near the right basal ganglion with severe perifocal edema (Figure **1**). Besides, he complained of headache, left facial palsy, nausea and vomiting in recent days. At our neuro-surgery outpatient department, surgical intervention was suggested to obtain the tissue pathology and diminish increased intracranial pressure status.

On the admission, his consciousness was clear but became slow in response. Neurological examination revealed left central facial palsy and left sided weakness (Muscle power = 3-4). We checked the serum tumor markers for differential diagnosis. The α-fetoprotein (AFP) level was 901.9 mcg/L and β-subunit of human chorionic gonadotropin (β-hCG) level was <0.5 U/L. Under the impression of intracranial NGGCTs

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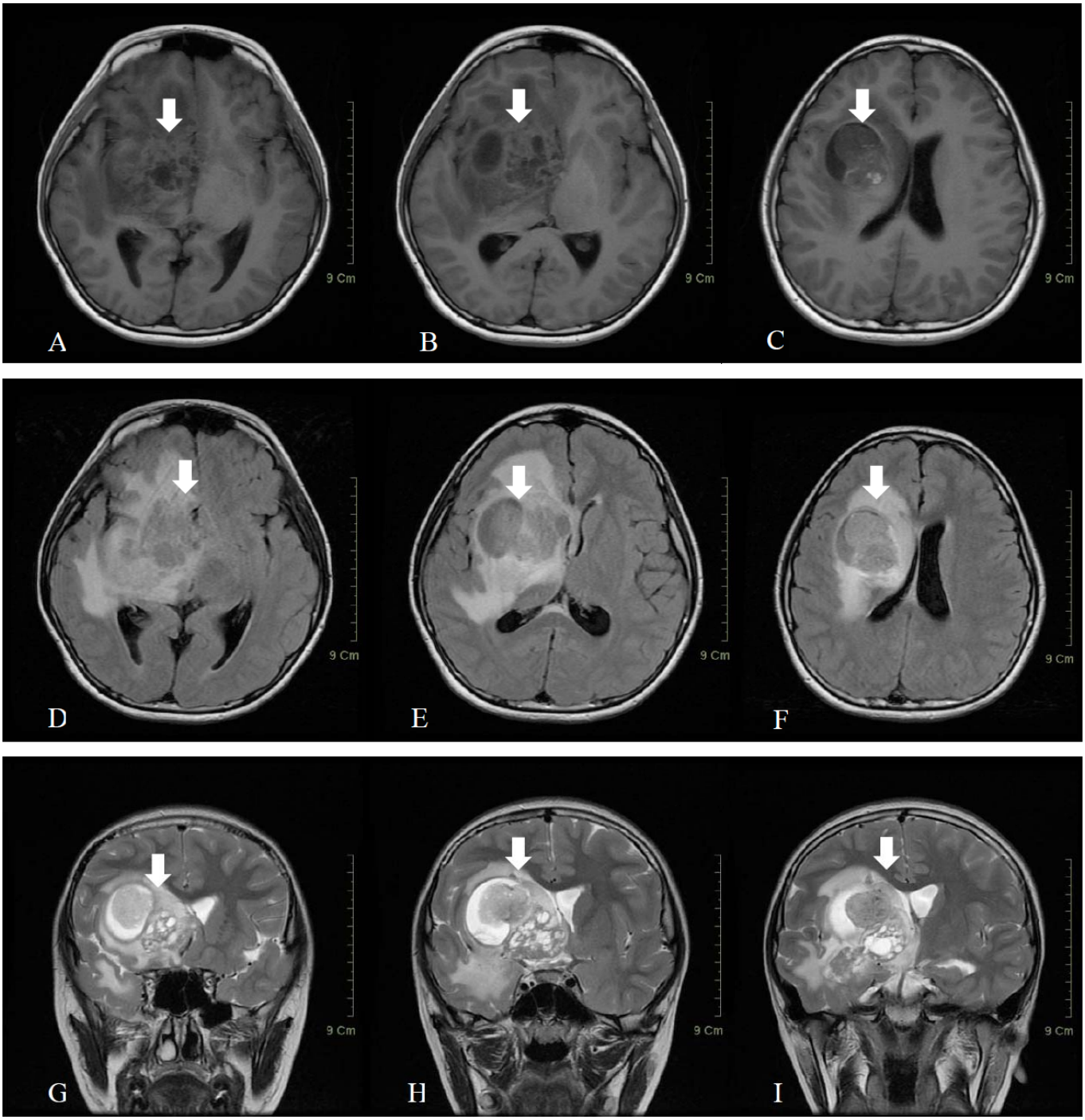


Figure 1: Pre-operation brain MRI images.

The images show a heterogeneous lesion at right basal ganglion area with midline shift, compression of the anterior horn of bilateral lateral ventricle, and perifocal edema. There are several cyst-like lesion (white arrow) with hypointensity on T1-weighted image (A-C, axial T1-weighted Flair image) and hyperintensity on T2-weighted image (D-F, axial T2-weighted Flair image). Old blood clot is suspected. A solid part (white arrow), about 5 cm in diameter over right frontotemporal area is also noted (G-I, coronal T2-weighted image).

with increased intracranial pressure, we performed right frontotemporal craniotomy with trans-sylvian, trans-insular approach for tumor resection under navigator assistance on February 18, 2009.

After dura opening, severe brain swelling was noted. Cisternostomy via pre-chiasma cistern was done for decompression firstly. Then, one yellow to brown colored tumor, about 8x6x5cm^3 in size was identified

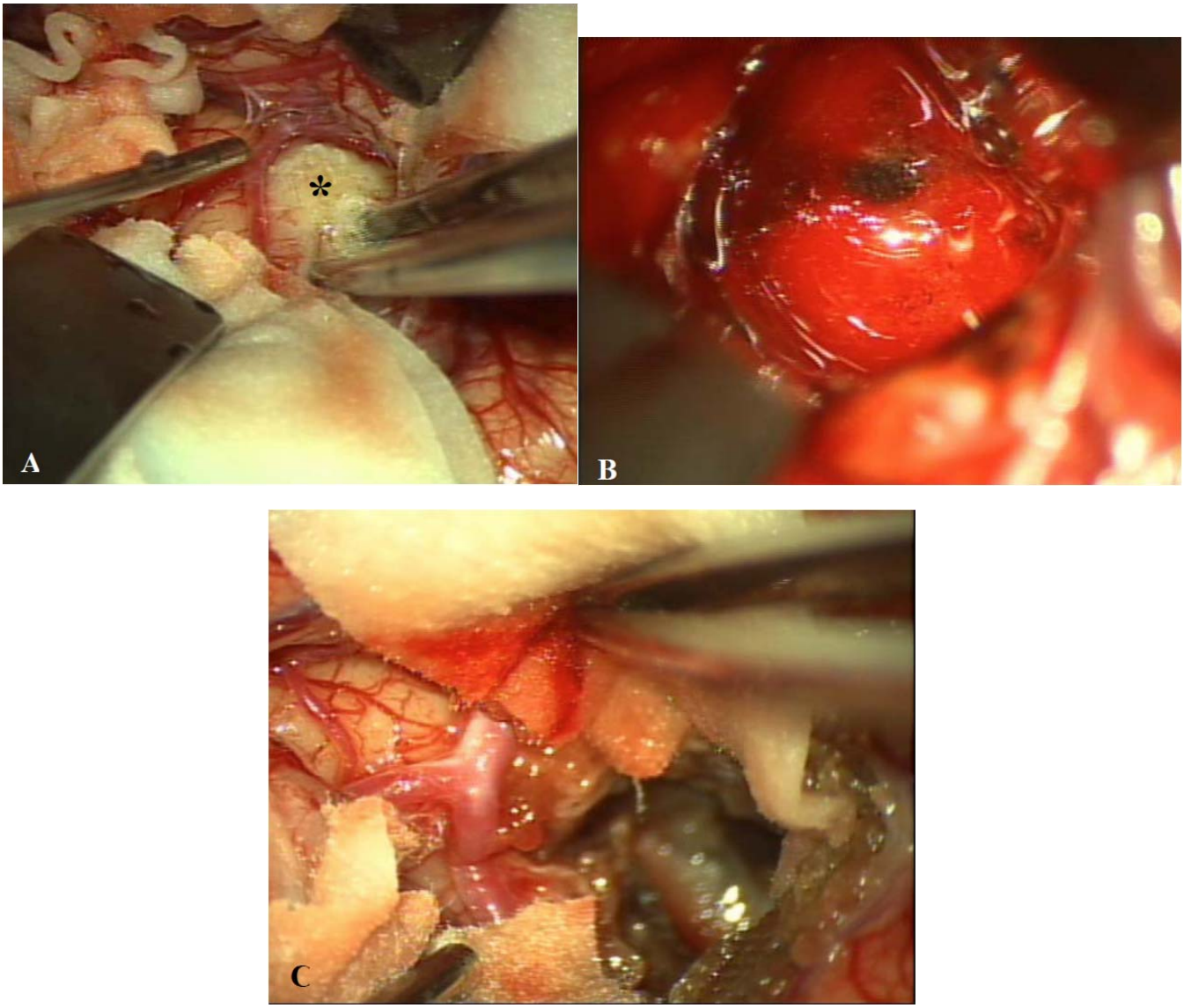


Figure 2: Intraoperative pictures by microscope. **A.** One yellow to brown color tumor, about 8x6x5cm^3 in size, localized over right basal ganglion is noted (*) after trans-Sylvian approach. A frontal branch of MCA is above the tumor. **B.** A cystic component with fresh blood clot. **C.** After grossly near total excision of the tumor.

near right basal ganglion with hypervascularity. We also found that there was a cystic component with fresh blood clot, probably related to the bleeding in the tumor. Frozen pathology showed choroid plexus carcinoma. Grossly near total resection was done and much brownish mucus content and old blood clots were found in the specimen (Figure **2**). The final pathological report revealed mixed germ cell tumor with primary yolk sac tumor component, characterized by tubulopapillary structures with vacuolated cuboidal cells, cystic spaces with eosinophilic hyaline bodies, and Schiller-Duval bodies. Some foci of germinoma components were also noted (Figure **3**). CSF cytology study was negative for malignancy.

The postoperative course was uneventful. We arranged the whole spine MRI and no evidence of spinal metastasis or CSF seeding was observed. He was transferred to pediatric hematologist for further chemotherapy with BEP (Bleomycin, Etoposide, and Platinum) on February 24, 2009 (POD 6) till September 8, 2009 (Total 6 courses). The AFP level decreased dramatically after operation and adjuvant chemotherapy (Table **1**). He also received whole brain radiotherapy since April 7, 2009 (POD 47) and completed on May 18, 2009 (Total 5400cGy/30 fractions). The recent brain MRI images showed no evidence of recurrence in August, 2013 (Figure **4**). Till now, he survived more than 5 years with Glasgow

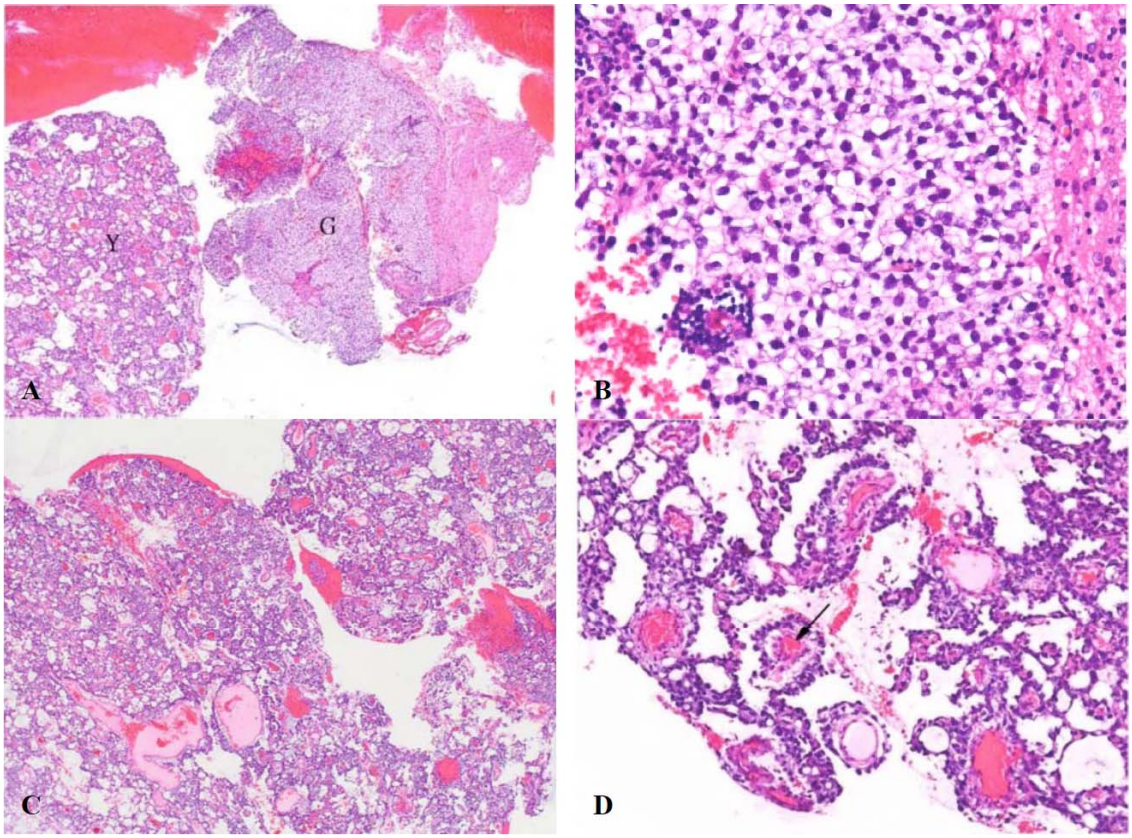
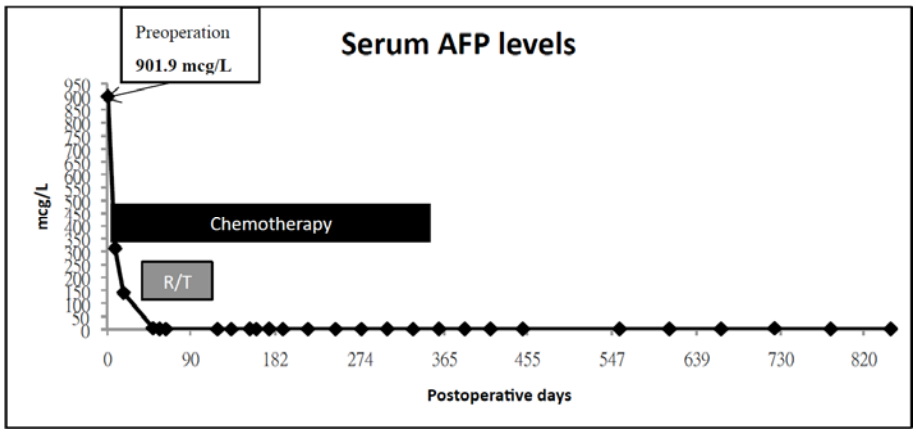


Figure 3: Histopathology of a specimen obtained from the tumor at right basal ganglion area. **A.** There are two components in the specimen (G: Germinoma ; Y: Yolk sac tumor). **B.** Section shows germinoma characterized by middle to large cells with abundant cytoplasm and round nuclei but varies in size and shape. **C.** Section shows yolk sac tumor characterized by tubulopapillary structures with vacuolated cuboidal cells, cystic spaces with eosinophilic hyaline bodies, and Schiller-Duval bodies (black arrow in D).

Table 1: Line Chart of serum AFP level in blood



outcome scale = 5 status and prepares to study in a university.

DISCUSSION

Germ cell tumors (GTCs) are one kind of neoplasm derived from germ cells. If there is no evidence of a primary tumor in either the testes or the ovaries, we call this kind of GCTs as extragonadal GCTs. Extragonadal GCTs typically arise in midline locations. In adults, the most common sites are the anterior mediastinum, retroperitoneum, and the pineal and suprasellar regions. In infants and young children, intracranial

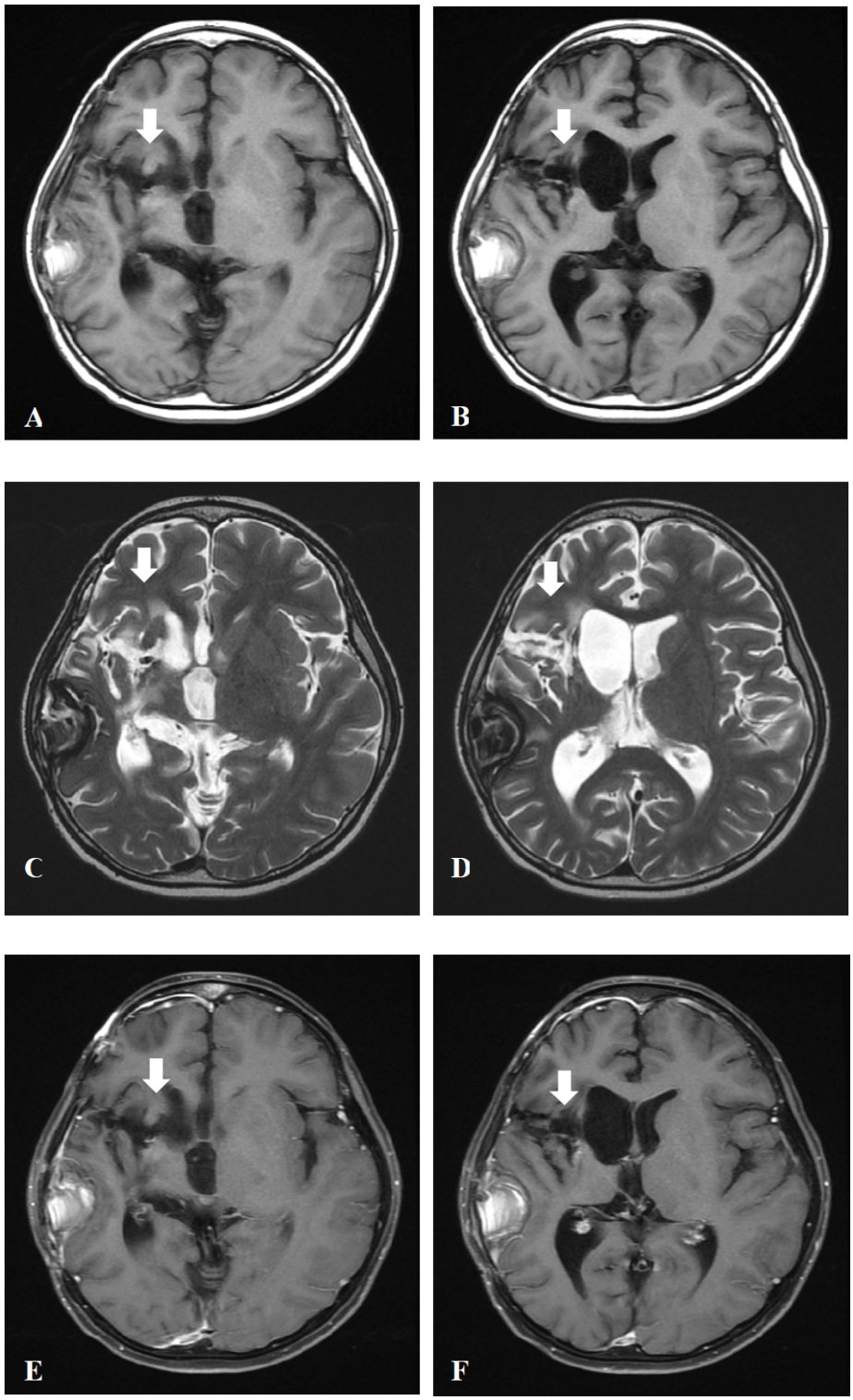


Figure 4: The followed brain MRI images on August 27, 2013, 4.5 years after operation. The MRI images of T1-weighted (A, B), T2-weighted (C, D) and T1 with contrast enhanced (E, F) showed the regional encephalomalacia over right basal ganglion area (white arrow), compatible with postoperative change. No evidence of tumor recurrence is mentioned.

GCTs and sacrococcygeal teratomas are more common than other locations. The two most frequent sites of pediatric intracranial GCTs raised from are the pineal gland (48%) and the suprasellar regions (37%). The prevalence rate of GCTs in the basal ganglion and thalamus is estimated lower than 14% of all intracranial GCTs [1, 3].

Primary central nerve system (CNS) GCTs are relative a rare disease. The incidence rate in Western countries is 0.1 per 100000 person-years. The male/female ratio is variable and higher when the tumor located in the pineal body (15:1) and just near 1:1 when the tumor located in the suprasellar region [4]. However, there are higher incidence rates in Japan and South Korea reported in previous studies [1, 5-8]. But, the recent data showed that there is no significant difference of the incidence rates between Japan (males = 0.143; females = 0.046) and United states (males = 0.118; females = 0.030). Approximately 90% primary CNS GCTs occur before the age of 20 years. The peak incidence is around 10-19 years of age [4].

According to the World Health Organization (WHO) classification, GCTs can be divided into two subgroups, germinomas and non-germinomatous GCTs (NGGCTs), histologically. The NGGCTs group includes embryonal carcinoma, endodermal sinus tumor, choriocarcinoma, teratoma (immature and mature), and mixed tumors with more than one element [1, 9] (Table **2**). In the European classification systems, the GCTs are divided into non-secreting group and secreting group according to if the serum or CSF presents the tumor markers. The most common tumor markers presenting in NGGCTs are α-fetoprotein (AFP) and β-subunit of human chorionic gonadotropin (β-HCG). If the tumors present with an elevated CSF AFP≥10 ng/ml and/or a CSFβ-HCG level>50 IU/l or greater than the accepted laboratory normal range, they are defined as a secreting tumor (Table **3**)[10]. By the WHO classification, the case that we reported is a primary yolk sac tumor (endodermal sinus tumor) with some geminoma components and localized at an unusual site.

Table 2: World Health Organization Classification of Intracranial Germ Cell Tumors and Prevalence Rates

Germinomas (60-65%)
Nongerminomatous germ cell tumors
Embryonal carcinoma (5%)
Yolk sac tumor (endodermal sinus tumor) (7%)
Choriocarcinoma (5%)
Teratoma (18%)
Bening teratomas
Immature
Mature
Teratoma with malignant transformation
Mixed germ cell tumors

Table 3: European Classification of Intracranial Germ Cell Tumors

Non-secreting
Pure germinoma
Mature teratoma
Secreting *(CSF AFP positivity > 10 ng/ml and/or CSF b-HCG elevations > 50 IU/l or above the laboratory's normal range)*
Non-germinomatous germ cell tumors (NGGTCs)

The clinical symptoms of patients with intracranial GCTs depend on the location of the tumor. When tumor is localized at pineal gland, obstructive hydrocephalus and signs of increased intracranial pressure are noted usually. If the tumor is localized at suprasellar regions, the most common sympyom is hypothalamic or pituitary dysfunctions, including diabetes insipidus, delayed pubertal development or precocious puberty, isolated growth hormone deficiency, or other aspects of hypopituitarism. In our case, the initial symptom of the patient was left side weakness. According to previous studies, the major symptoms of basal ganglion or thalamus GCTs are hemiparesis, mental deterioration such as dementia or character change, precocious puberty, diabetes insipidus, oculomotor palsy, speech disturbance, and hemianopsia [3]. The reason is the same as tumors at pineal gland or suprasellar regions, mass effect of the tumor, hemorrhage or perifocal edema causing the dysfunction of basal ganglion, thalamus, and nucleus of cranial nerve.

Magnetic resonance imaging (MRI) is the most preferred imaging technique for diagnosis and staging of the intracranial GCTs. The solid parts of GCTs were nearly isointense with grey matter on both T1- and T2-weighted images [11]. The MRI signal intensity reveals heterogeneous on T1- and T2-weighted images when there are components of hemorrhage, cysts or solid portions [12]. Focus on the yolk sac tumors, the shape is always irregular and perifocal edema is observed in some cases. Beside the morphology, the distinction between germinomas and NGGCTs is more critical, since children with germinomas have a more favorable prognosis and require less intensive therapy than those with NGGCTs. An elevated level of AFP in either the CSF or serum is sufficient to classify a tumor as a NGGCT. Any GCTs with an elevated AFP (>10 microg/L or higher than the institutional normal range) can be assumed to contain elements of endodermal sinus tumor or immature teratoma. Pure endodermal sinus tumor are often associated with dramatic elevations in AFP (>500 mcg/L), whereas immature

teratomas have less elevations of AFP and/or beta-hCG (Table **4**).

Table 4: Tumor Markers Expression of GCTs

Tumor type	Marker			
	β-HCG	AFP	PLAP	c-Kit
Pure germinoma	-	-	+/-	+
Yolk sac tumor	-	+	+/-	-
Choriocarcinoma	+	-	+/-	-
Embryonal carcinoma	-	-	+	-
Mixed GCT	+/-	+/-	+/-	+/-
Mature teratoma	-	-	-	-
Immature teratoma	+/-	+/-	-	+/-

Finally, histological examination is necessary to establish a definitive diagnosis of an intracranial GCT and to ascertain the histological subtype. A tissue sample should be obtained by surgery, but surgical biopsies offer only a small sample and may lead to an inaccurate tissue diagnosis. So, when the tissue diagnosis is discordant from the CSF or serum markers, treatment should be based on the result that is associated with the most malignant histology and worst prognosis.

Pediatric intracranial germinomas are exquisitely sensitive to the radiation therapy. Most contemporary series have reported long-term progression free survival (PFS) rates >90 percent for children with localized and pure germinomas after radiation therapy alone [13]. On the other side, NGGCTs are less common than germinomas and includes several histological subtypes. So, available clinical data are sparse and difficult to interpret. In the absence of a prospective randomized study, chemotherapy followed by radiation therapy remains the standard of care for the children with intracranial NGGCTs [14].

Neurosurgical intervention is useful for diagnosis, tumor cytoreduction or tumor related hydrocephalus. The role of maximal surgical resection is still indefinite. One retrospective analysis suggests that multimodal treatment, combing total surgical resection, chemotherapy, and radiation therapy is necessary for NGGCTs, especially for poor prognosis group (Choriocarcinoma, Yolk sac tumor, Embryonal carcinoma, Mixed tumors mainly composed of choriocarcinoma, yolk sac tumor, or embryonal carcinoma) [15]. But which is the optimal management: the radical resection with adjuvant chemotherapy or the radiation therapy and neoadjuvent therapy with residual tumor resection the large randomized control trials are still lacking [16].

In the recent studies, the treatment for intracranial NGGCTs is usually a combined therapy, including surgical debulking, high dose radiotherapy (RT) and chemotherapy (CT) [4, 17]. Within the safe range, radical removal is preferred to biopsy only or subtotal resection for more precise histological classification and maximal chance of survival [18]. Biopsy can only provide one small part of the whole tumor and may confound a mixed tumor with germinoma, resulting in a wrong therapeutic strategy. Some studies have shown that more aggressive resection for NGGCTs can improve the tumor control rate [19, 20].

Treatment of NGGCTs with RT or CT alone has been associated to a poor long-term outcome, but they played important roles in multi-modal treatment [21-24]. Patients with NGGCTs other than mature and immature teratomas who receive RT at a dose of > 50 Gy have significantly higher survival as compared to patients who do not receive RT or lesser RT dose. Administrations of chemotherapy to these patients are also related to significantly improved survival rates [18]. The most effective agents include bleomycin, cisplatin, carboplatin, etoposide, ifosfamide, and vinblastine. Neoadjuvant chemoradiotherpay before tumors resection is reported to dramatically improve the prognosis of pediatric patients with NGGCTs [16, 25]. But in patients with increased intracranial pressure status or hydrocephalus related neurological deficit, urgent surgical intervention plus adjuvant chemoradiotherpay is more preferred to prevent severe neuron damage caused by post-RT brain swelling.

In our case, although the tumor was located in the basal ganglion, we did the surgical debulking with microsurgical technique and navigational guidance to reach the maximal resection and leave the minimal sequelae. At post-operative follow up, he only received one course of whole brain radiotherapy (Total 5400cGY) and chemotherapy (Bleomycin, Etoposide, and Platinum for 6 times). No evidence of tumor recurrence has been found for more than five years in series MRI images and AFP levels. In our opinion, the first surgical planning and intervention decide about the disease progression and prognosis, as we treat glioblastoma, especially for the poor prognosis group of NGGCTs. How to reach the maximal tumor resection and avoid the eloquent areas damage are the most important things to consider for a neurosurgeon to treat NGGCTs.

CONCLUSION

The NGGCTs localized at basal ganglion is relative unusual. Because of the rarely seen location, the clinical characters become untypical and difficult to diagnosis. Although there are several reports suggest that neoadjuvent chemotherapy and radiation therapy followed by complete residual tumor resection is highly effective [26-27]. We performed a near total tumor resection to relieve increased intracranial pressure status emergently, and then combined adjuvant chemotherapy and radiation therapy in this case. No tumor recurrence is noted for more than 5 years, and the patient has good development without neurological sequelae. Therefore, the long-term effect of maximal surgical resection with adjuvant chemotherapy and radiation therapy may have an important position in treatment of NGGTS and is still needed to be explored through further clinical studies.

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