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# Successful Treatment of Intracranial Germ Cell Tumor: Report of Two Unusual Cases and Literature Review

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**Key Words**
Germinoma · Choriocarcinoma · Intracranial germ cell tumor · Chemotherapy · Radiation therapy

**Abstract**
Primary intracranial germ cell tumor (GCT) is a rare tumor that generally occurs due to developmental anomaly. Although intracranial GCT is sensitive to treatment, a high recurrence rate, treatment-related long-term complications and the heterogeneity of this tumor group make treatment complicated. Moreover, because of its location, hydrocephalus and visual field defect, functional disturbance of the pituitary gland can occur and require attention. Treatment primarily relies on chemotherapy and radiation therapy but the management of intracranial GCT remains unsettled, especially in the case of unusual circumstances such as multifocal tumor or nongerminomatous GCT. Here, we present two unusual cases of intracranial GCT: one case with a bifocal intracranial germinoma, and the other with an intracranial choriocarcinoma. Both cases were treated with neoadjuvant chemotherapy followed by reduced-field radiation therapy without significant treatment-related complication. Further, we performed a PubMed search to investigate the appropriate treatment strategy for this unusual subtype of intracranial GCT.





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## Introduction

Primary intracranial germ cell tumor (GCT) is a rare subset of intracranial tumors. They are known to occur primarily in the 2nd and 3rd decades of life and arise from the midline structure, especially the pineal gland or suprasellar region due to aberrant migration during embryogenesis. Although intracranial GCT is known to show a high cure rate because of its sensitivity to radiation and chemotherapy, there are several points to be considered, especially in unusual cases. Here, we report two unusual cases of intracranial germinoma (1 germinoma and 1 chriocarcinoma). Induction chemotherapy with 4 cycles of ifosfamide, carboplatin and etoposide combination chemotherapy showed a remarkable response without complications in both patients.

## Case Report

*Case 1*

A 16-year-old male without a past medical history presented to our hospital due to headache and diplopia. An initial brain magnetic resonance image (MRI) revealed a well-enhanced 3.8 × 2.7 cm sized multicystic mass in the pineal gland with hydrocephalus (fig. 1a). Laboratory findings revealed that serum β-human chorionic gonadotropin (HCG) was increased to 19,920 mIU/ml, and the α-fetoprotein level was 3.6 ng/ml. Craniotomy was performed for tumor removal, as well as external ventricular drainage. However, on the operation field, a hypervascular tumor was recognized. Given the risk of bleeding, a minimal tissue biopsy with ventricular drainage was performed. The pathologic result of the biopsy was choriocarcinoma. Cytologic examination of the drained cerebrospinal fluid did not find any malignant cells. A whole-body positron emission tomography/computed tomography (PET-CT) scan did not reveal any lesions, including the mediastinum and gonad. Concerning hemorrhagic complication, systemic chemotherapy was chosen as initial treatment rather than radiation therapy. Ifosfamide (900 mg/m$^2$ on days 1–5), cisplatin (20 mg/m$^2$ on days 1–5) and etoposide (50 mg/m$^2$ on days 1–5) combination chemotherapy was administered. After 2 cycles of chemotherapy, complete regression of the intracranial mass was identified without complication (fig. 1b). The serum β-HCG level was normalized to 0.27 mIU/ml. After an additional 2 cycles of chemotherapy, radiation therapy covering the entire ventricular system and the spine was performed for consolidation purpose. He tolerated the entire treatment without specific complications.

*Case 2*

A 17-year-old male without a previous medical history presented with headache, vomiting, polydipsia and polyuria. Initial brain MRI revealed two well-enhanced T1 and T2 isointense masses in the suprasellar region and pineal gland (fig. 2a, c). Laboratory findings showed serum α-fetoprotein (1.1 ng/ml) and β-HCG (1.56 mIU/ml) levels within the normal range. Despite increased serum osmolality, urine was diluted and polyuria was not corrected after water deprivation. The prolactin level was increased up to 77.65 ng/ml (range 1.1–13.0). During navigation-guided craniotomy with tumor biopsy, which was performed on the suprasellar mass, germinoma was confirmed. Sequential spine MRI and spinal tapping did not reveal any concomitant lesions on the entire spine. To reduce the radiation dose and field, upfront chemotherapy was decided on. Ifosfamide (1,800 mg/m$^2$ on days 1–5) and etoposide (100 mg/m$^2$ on days 1–3) combination chemotherapy was administered alternatively with etoposide (100 mg/m$^2$ on days 1–3) and carboplatin (600 mg/m$^2$ on day 1). He

completed 4 cycles of neoadjuvant chemotherapy without specific treatment-related complications; however, grade 4 hematologic toxicity was identified. After 4 cycles of chemotherapy, complete regression of all masses on both lesions was identified (fig. 2b, d). Consolidative radiation therapy was performed on the whole ventricular system (24 Gy), and a boost dose of 16 Gy was irradiated to the tumor bed.

## Discussion

When planning the initial treatment strategy against intracranial GCT, pathological subtype and disease extent (especially spinal metastasis) are the most important factors. In general, germinoma shows high radiosensitivity and excellent prognosis. Thus, radiation alone can be considered as treatment. Although the treatment strategy against germinoma, which is a major component of intracranial GCT, is relatively well established, in the case of a rare pathologic subtype other than germinoma or uncommon clinical presentation, such as bifocal disease, optimal treatment has not yet been settled. Moreover, although craniospinal irradiation (CSR) has traditionally been considered as the gold standard of treatment against intracranial germinoma, concern about late neurologic detrimental effects of CSR, especially in young patients, led physicians to omit spinal irradiation and try to reduce the radiation field as much as possible in limited disease [1]. As a result, multimodality therapy including preirradiation chemotherapy was attempted. Firstly, a few prospective studies of the SFOP (French Pediatric Oncology Society), COG (Children's Oncology Group) and SIOP (International Society of Pediatric Oncology) showed the feasibility of upfront chemotherapy in intracranial germinoma. However, the facts that chemotherapy alone cannot replace radiotherapy and that the radiation volume should include at least the whole ventricular system remain unchanged [2]. To reduce complications of radiation treatment and improve treatment outcome in intracranial germinoma, the appropriate role of chemotherapy should be further studied. In the case of nongerminomatous GCT (NGGCT), the significance of chemotherapy increase and multimodality treatment is mandatory. NGGCT is known to have a poor prognosis and a high recurrence rate compared with the germinoma-like gonadal counterpart tumor. In practice, many retrospective studies demonstrated that treatment with radiation alone in NGGCT showed high relapse rates and shorter recurrence-free survival. In addition, the superiority of combined modality therapy over treatment with radiation alone in NGGCT has been proposed by several landmark studies such as the SIOP-CNS-GCT 96 trial and the Japanese cooperative study [3, 4].

Although the importance of chemotherapy in the treatment of intracranial GCT was recognized, there is no standardized chemotherapeutic protocol, which includes the fine details about pathologic subtype, dosage, treatment duration and temporal sequence with radiation therapy. The chemotherapeutic agents were selected primarily based on the experience in gonadal GCT treatment. Based on previous reports about chemotherapy against intracranial GCT, methotrexate, ACNU, vinblastine, vincristine, bleomycin, ifosfamide, etoposide and carboplatin/cisplatin have been used as main chemotherapeutic agents. Recently, many institutions have preferentially used etoposide, ifosfamide and cisplatin, but the administration schedule is inconsistent. On some occasions, etoposide and ifosfamide were used alternatively with a platinum agent and, in other cases, all 3 agents were used at once. In a few case reports, even concomitant chemoradiation therapy was used. Therefore, we performed a PubMed search for induction chemotherapy of intracranial GCT to organize chemotherapeutic regimens systematically. In addition, we searched the literature for treatment strategies

performed in unusual cases, such as bifocal intracranial germinoma and primary intracranial choriocarcinoma (PICCC).

Based on one international CNS GCT study [5], which intended to demonstrate the efficacy of a chemotherapy only strategy, chemotherapy intensity was shown to be quite strong. In low-risk patients, carboplatin (1,200 mg/m$^2$)/etoposide (450 mg/m$^2$) and cyclophosphamide (4 g/m$^2$)/etoposide (450 mg/m$^2$) were administered alternatively, and response evaluation was performed every 2 cycles. If patients achieved complete response, radiation therapy was not performed, and if patients did not achieve complete response after 4 cycles of chemotherapy, surgical resection with pathologic evaluation to exclude teratoma or high-dose myeloablative chemotherapy with autologous hematopoietic cell rescue was considered. In high-risk patients, including those with NGGCT, the 3-drug regimen consisting of carboplatin, cyclophosphamide and etoposide was administered at once. Sequential treatment strategy was identical with low risk. However, according to these regimens, grade III and IV hematologic toxicity occurred in >90% of patients. The 6-year event-free survival was 27.3% in the low-risk and 50% in the high-risk group. Consequently, this study demonstrated the toxicity of high-dose chemotherapy; nevertheless, the effect of the 3-drug regimen in the high-risk group including NGGCT was favorable and worth considering a neoadjuvant chemotherapy regimen [5]. In the study of Kochi et al. [4], the intensity of the chemotherapy was attenuated. In the low-risk group, cisplatin (20 mg/m$^2$) and etoposide (60 mg/m$^2$) were administered, and in the group with a poor prognosis, ifosfamide (900 mg/m$^2$), cisplatin (20 mg/m$^2$) and etoposide (60 mg/m$^2$) were administered for 5 consecutive days. Usually, 3 cycles were performed before radiation therapy. Although enrolled patients were small in number, the outcome was encouraging. Although many other regimens have been reported, there was no report which compared various neoadjuvant chemotherapy regimens in terms of efficacy and toxicity due to the paucity of intracranial GCT. Therefore, we also used this regimen for our two cases.

Whereas most patients who have been diagnosed with intracranial GCT present with a single mass, about 5–25% of the patients present with synchronous lesions in both the pineal gland and neurohypophyseal region, and these patients have been described as 'bifocal' or 'multicentric', distinguished from disseminated GCT. However, it remains uncertain whether these lesions are truly synchronous or metastatic lesions. Until now, many authors have put more weight on synchronous lesions rather than on metastasis. Many previous studies have supported this theory by showing a favorable outcome of bifocal intracranial GCT to limited field irradiation [6]. However, some authors insist that these patients also impose a risk of dissemination, proposing results that bifocal GCT showed a significantly shorter event-free and overall survival than germinoma from a single site of origin [7]. Moreover, because bifocal lesions are not an exclusive sign of germinoma and performing a biopsy from both sites is not feasible, the possible presence of a nongerminomatous component cannot totally be excluded [8]. Therefore, in bifocal GCT, a multimodal treatment strategy including neoadjuvant chemotherapy, even in the case of germinoma which has been pathologically confirmed on either site, would be reasonable. However, if the tumor marker, such as β-HCG, does not strongly imply NGGCT, an intensive regimen will not be suitable. In conclusion, neoadjuvant chemotherapy with an alternating chemotherapy regimen consisting of two drugs followed by reduced field irradiation is thought to be reasonable, like in our case.

PICCC is a very rare but most malignant subtype of intracranial GCT, with a few unique features which make treatment complicated. Based on a clinical study on 66 PICCC cases (including mixed GCT) [9], the median survival time was just 22 months, and fatal complications such as tumor hemorrhage and cerebrospinal fluid metastasis were more frequent than in other types of intracranial GCT. Especially, tumor hemorrhage occurred in 22 of 66

cases, and some of them were associated with catastrophic consequences. Furthermore, 5 cases with hemorrhages were caused by radiation therapy whereas no case of hemorrhage was identified during chemotherapy. Due to the hemorrhagic tendency of choriocarcinoma, upfront surgical resection is difficult and, sometimes, even biopsy confirmation is omitted in practice. Many oncologists have been interested in the incidence of hemorrhagic complications and how to reduce them, and the opinion that radiation therapy can provoke tumor hemorrhage has been proposed. Although there were 2 reports which treated PICCC with concurrent chemoradiation therapy [9, 10], considering the potential hemorrhagic complications by radiation and treatment-related bone marrow toxicity, a more careful approach is required. For the chemotherapeutic regimen, a platinum-containing regimen has been used with favorable outcomes, like in other subtypes of NGGCT. The previous two studies also used a combination chemotherapy consisting of ifosfamide, cisplatin and etoposide as one of the mainstay of treatment. In conclusion, neoadjuvant chemotherapy consisting of 3 drugs followed by CSR or reduced field radiation therapy is thought to be reasonable, like in our case.

## Statement of Ethics

We declare that the all patients gave oral consent to publishing this case report. Further, this case report was approved by our Institution's Ethics Committee.

## Disclosure Statement

The authors declare that they have no competing interests.

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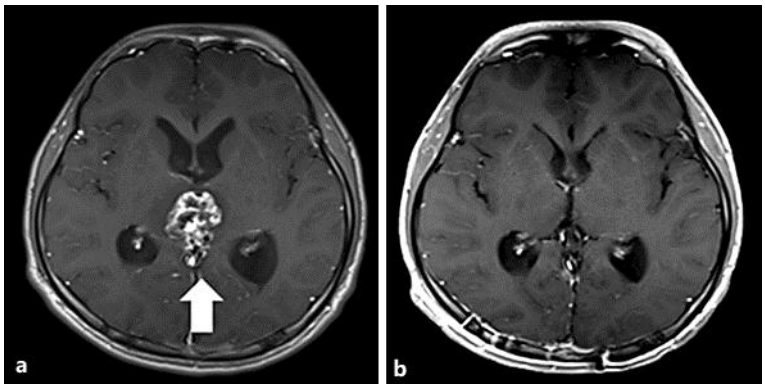


**Fig. 1.** **a** Initial brain MRI showing a lobulated mass of about 3.8 × 2.7 × 2.5 cm at the pineal region with hydrocephalus (arrow). **b** No evidence of any remnant mass after 2 cycles of chemotherapy.

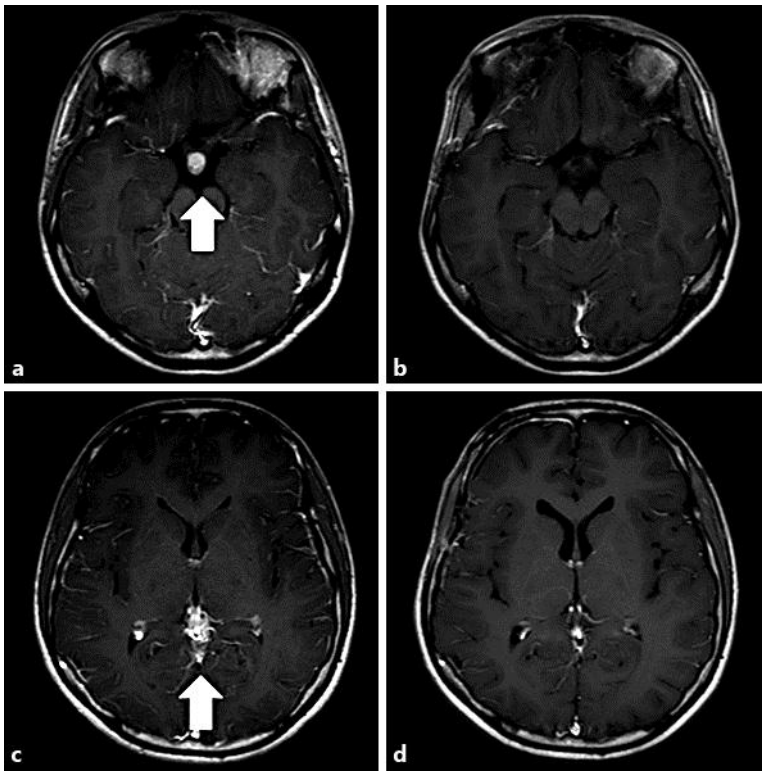


**Fig. 2.** **a** A T1 and T2 isointense nodular lesion of about 1.0 × 0.8 cm with strong enhancement at the suprasellar cistern (arrow). **b** No definite remaining enhancing lesion in the suprasellar region. **c** A T1 and T2 isointense nodular lesion of about 1.1 × 1.6 cm with strong enhancement at the pineal gland (arrow). **d** Near complete regression of the enhancing mass in the pineal gland.