Spontaneous Regression in Intracranial Germinoma: Case Report and Literature Review

Si Zhang, Qiang Li, Yan Ju

BACKGROUND: **Spontaneous regression in intracranial germ cell tumors (GCTs) is an extremely rare phenomenon with only 9 cases reported. The mechanism and natural history of this phenomenon are still equivocal.**

METHODS: **A 12-year-old boy presented with a lesion in the suprasellar region with involvement of basal ganglia and corpus callosum. After 1 month, his symptoms were relieved, and magnetic resonance imaging demonstrated a remarkable regression of the lesion. Three months later, the boy's symptoms deteriorated, and magnetic resonance imaging revealed regrowth and enlargement of the lesion. Diagnosis of germinoma was confirmed via biopsy, and radiation therapy achieved complete response. We performed a systematic literature review of spontaneous regression of intracranial GCTs. The natural history of these cases was analyzed, and hypotheses in the studies were discussed.**

RESULTS: **Spontaneous regression is extremely rare with only 10 cases reported, including the present case. There were 9 male patients and 1 female patient with mean age 22.1 ± 10.3 years (range, 12–43 years). Nine cases were diagnosed as germinoma, and 4 cases included an episode of regression followed by regrowth. The mechanism of tumor regression in intracranial GCTs remains unclear. Four hypotheses were proposed, including radiation exposure, surgical procedures, effects of steroids, and immune reaction triggered by intervention.**

CONCLUSIONS: **Tumor regression in intracranial GCTs could be a iatrogenic transient phenomenon, caused by complex immune reactions triggered by interventions.**

INTRODUCTION

Spontaneous regression of testicular germ cell tumors (GCTs), also known as burned-out or shrinking seminomas, is a well-recognized phenomenon.[1] As a counterpart of gonadal GCTs, intracranial GCTs manifesting with spontaneous regression are extremely rare with only 9 cases reported.[2-10] Although several hypotheses, including irradiation, surgical trauma, and effects of steroids, have been proposed, the mechanism and natural history of spontaneous regression are still unknown. We report a rare case of a patient with disseminated intracranial germinoma who experienced significant tumor regression and regrowth in a period of 4 months. Additionally, we present a review of the literature and discuss the mechanism of tumor regression in intracranial germinomas.

MATERIALS AND METHODS

Case Report

A 12-year-old boy was referred to our hospital with progressive blurred vision accompanied by right-sided hemiparesis over a period of 6 months and headache for 1 month. Magnetic resonance imaging (MRI) at the local hospital (performed July 23) revealed a massive lesion located in the suprasellar region with involvement of left basal ganglia, septum pellucidum, and corpus callosum (**Figure 1A–C**). Examination of tumor markers, including alpha fetoprotein and beta human chorionic gonadotropin, in serum and cerebrospinal fluid was normal. After intravenous infusion of glycerol and methylprednisolone (40 mg/day) for 3 days, the patient was referred to our department for elective surgery. On admission to our department, the patient's symptoms improved, and preoperative MRI (performed August 19) showed a remarkable tumor regression >80% in tumor size (**Figure 1D–F**). Stereotactic

Key words
- Germinoma
- Iatrogenic
- Spontaneous regression

Abbreviations and Acronyms
CT: Computed tomography
GCT: Germ cell tumor
MRI: Magnetic resonance imaging

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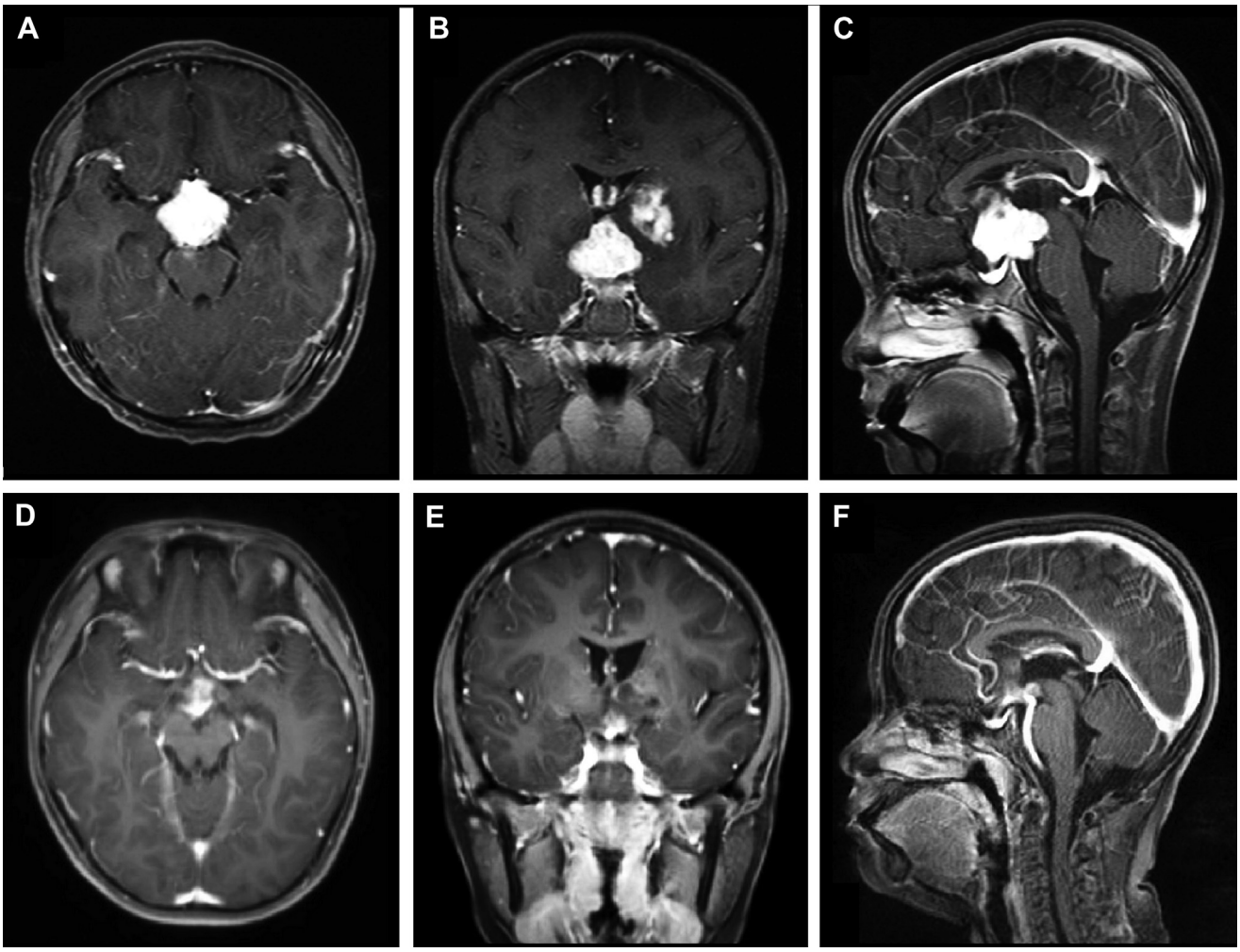

Figure 1. (**A**–**C**) Magnetic resonance imaging obtained in the local hospital revealed a homogeneously enhanced lesion located in the suprasellar region with involvement of left basal ganglia, septum pellucidum, and corpus callosum. (**D**–**F**) One month after detection of the lesion, repeat magnetic resonance imaging showed remarkable regression of the lesion.

biopsy was recommended to confirm the pathologic diagnosis; however, the patient's parents refused biopsy and chose observation. The patient was readmitted to our department 3 months later with deterioration of his symptoms. MRI demonstrated regrowth and enlargement of the lesion with hydrocephalus (Figure 2A–C). Examination of tumor markers was still negative. A stereotactic biopsy was performed, and pathologic examination revealed small amount of large neoplastic cells admixed within a lymphoid-rich background. Immunohistochemistry revealed OCT3/4 and placental alkaline phosphatase positive with MIB-1 30%, which confirmed the diagnosis of germinoma. Abdominal computed tomography (CT) scan precluded the existence of gonadal GCT. Eventually, whole-brain irradiation at a dose of 24 Gy with a boost to the primary tumor site for a total of 45 Gy was performed. The patient recovered uneventfully and had a complete response to radiation therapy. During 5 years of follow-up, he remained recurrence-free (Figure 2D–F).

Literature Review

This study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.

Search Strategy and Article Selection. A computerized search strategy using the PubMed/MEDLINE database to identify relevant studies on spontaneous regression of intracranial GCTs was performed. The search included only articles in English published until June 2019 with no early date limit. We used combined key words and Medical Subject Headings as search terms for abstract and full

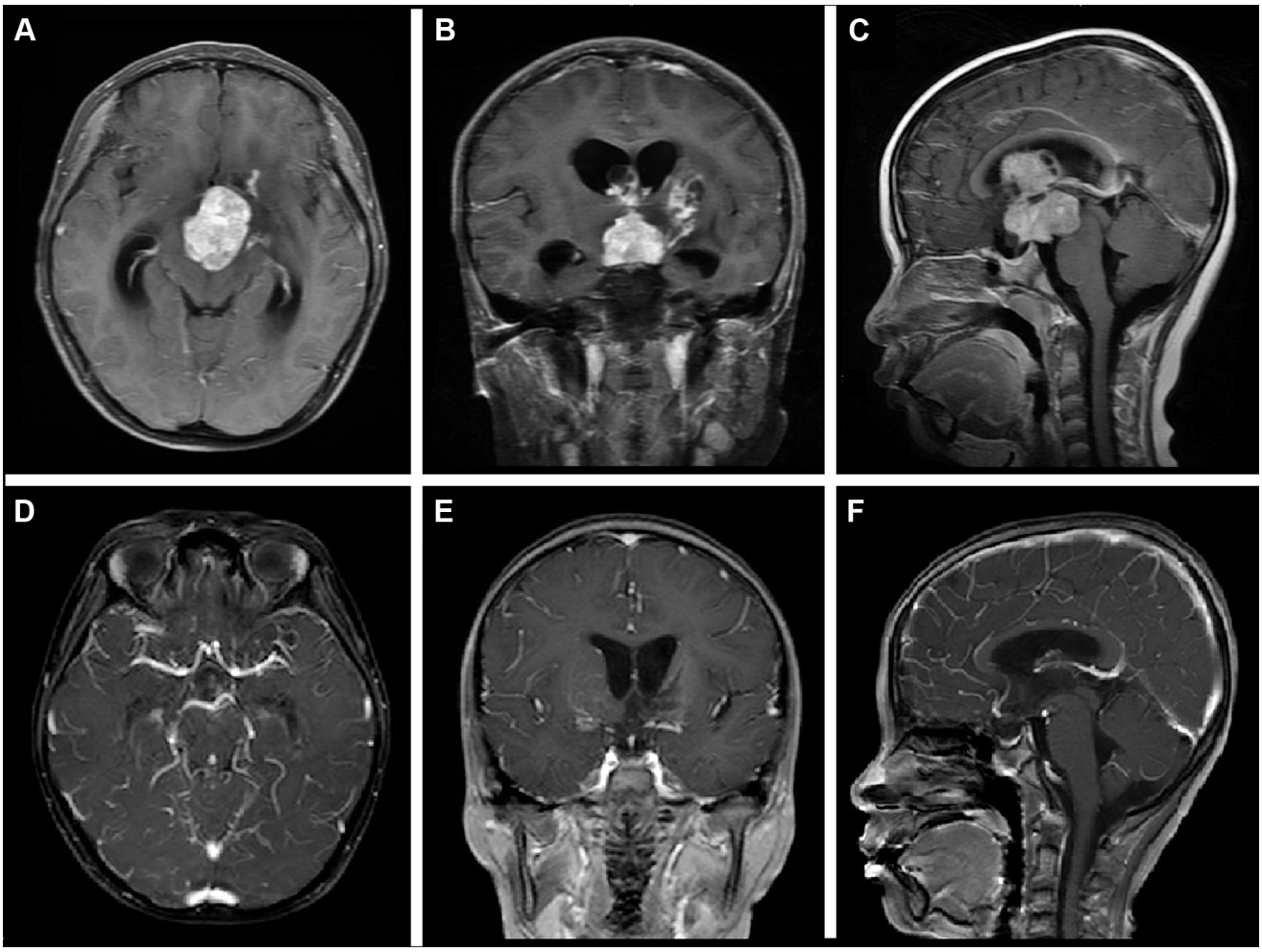

Figure 2. (**A**–**C**) After 3 months of observation, enhanced magnetic resonance imaging revealed regrowth and enlargement of the former lesion with obstructive hydrocephalus. (**D**–**F**) Magnetic resonance imaging during follow-up showed the lesion had disappeared.

text. The following terms were used: regression, shrinkage, germinoma, germ cell tumors, intracranial, spontaneous.

Titles and abstracts of all articles were screened. Only articles describing cases of spontaneous regression of intracranial GCTs were selected. Articles published in languages other than English were excluded from the study. References from relevant reviews were hand-searched. Subsequently, relevant articles were retrieved and evaluated independently by 2 authors (S.Z. and Q.L.) using EndNote X7 software (Thomson Reuters, Carlsbad, California, USA). A cross-reference check of the citations of each included relevant article was done to ensure that no relevant studies were missed by the computerized database search. Disagreements regarding inclusion of studies were resolved by discussion and consensus agreement.

Data Extraction. Two authors (S.Z. and Q.L.) independently of each other extracted the following characteristics from the included studies: setting, study type, demographic data of presented patients, surgical and other treatments performed, neurologic status, radiologic findings, pathologic diagnosis, and discussed hypothesis for regression.

RESULTS

Our search identified 27 potential citations for full-text evaluation. We excluded studies of animals, studies of other intracranial tumors, and studies in languages other than English. Nine cases of spontaneous regression of intracranial GCTs from 9 different publications between 1997 and 2018 could be extracted from the literature and matched the inclusion criteria of our study.

All cases are listed in **Table 1**. In 9 cases, the diagnosis was germinoma, and in 1 case, embryonal carcinoma was the diagnosis.[9] There were 9 male patients and 1 female patient with a mean age of 22.1 ± 10.3 years (range, 12–43 years). The most common symptoms were headache, a sign of intracranial

Table 1. Reported Cases of Intracranial Germ Cell Tumors Manifesting with Tumor Regression

Case	Reference	Age (Years)/Sex	Symptoms	Location	Tumor Markers	Pathology	Operation Before Regression	Steroid Before Regression	Radiation Before Regression	Hypotheses for Regression
1	Ide et al., 1997[6]	21/M	Headache and diabetes insipidus	Suprasellar region	Negative	Germinoma	VP shunt	No	CT (1)	Surgical procedure
2	Mascalchi et al., 1998[9]	18/F	Diabetes insipidus and galactorrhea	Suprasellar region and basal ganglia	NA	Embryonal carcinoma	No	Prednisone	CT (≥1)	Steroids
3	Fujimaki et al., 1999[3]	39/M	Headache, Parinaud syndrome, seizures, and stupor	Pineal region and cerebellar vermian	Negative	Germinoma	Resection of vermian lesion	Prednisolone	Plain x-ray (1) and DSA (1)	Surgical procedure
4	Murai et al., 2000[2]	17/M	Headaches, vomiting, and Parinaud syndrome	Pineal region	NA	Germinoma	VP shunt	No	CT (6)	Immune reaction triggered by surgical procedure and radiation exposure
5	Masoudi et al., 2008[7]	17/M	Headache and visual deficit	Pineal region	NA	Germinoma	EVD and ETV	Dexamethasone	CT (2)	Steroids
6	Si et al., 2010[8]	18/M	Headaches, nausea, progressive neurologic deficit, unsteady gait, and Parinaud syndrome	Suprasellar and pineal region	Negative	Germinoma	Biopsy, EVD, and VP shunt	Dexamethasone	CT (≥1)	Steroids and surgical procedures
7	Yoneoka et al., 2011[5]	43/M	Memory problems and visual deficit	Pineal and suprasellar region, fourth ventricle	NA	Germinoma	No	No	CT (1) and DSA (1)	Radiation exposure
8	Ono et al., 2011[4]	15/M	Headache, diplopia, and visual deficit	Pineal region	Negative	Germinoma	Reservoir placement	No	CT (4) and DSA (1)	Radiation exposure
9	Woo et al., 2018[10]	21/M	Dizziness, vomiting, and diabetes insipidus	Pineal region, foramen of Monro, fourth ventricle	Negative	Germinoma	ETV and biopsy	Hydrocortisone	CT (4)	Radiation exposure
10	Present case	12/M	Headache, visual deficit, and hemiparesis	Suprasellar, basal ganglia, septum pellucidum, and corpus callosum	Negative	Germinoma	No	Methylprednisolone	CT (1)	Immune reaction triggered by interventions

M, male; VP, ventriculoperitoneal; CT, computed tomography; F, female; NA, not available; DSA, digital subtraction angiography; EVD, extraventricular drainage; ETV, endoscopic third ventriculostomy.

hypertension (n = 7 patients; 77.8%); Parinaud syndrome (n = 3 patients; 33.3%); visual deficit (n = 3 patients; 33.3%); and diabetes insipidus (n = 3 patients; 33.3%). Tumor markers were examined in 5 cases, and all were within normal range. Five patients had multiple lesions on CT or MRI, and 4 patients had a single lesion in the pineal (n = 3 patients) or suprasellar (n = 5 patients) region. In all the reported cases, patients had received diagnostic irradiation before tumor regression, including repeated CT scans (1–6 times) and angiography. Among these cases, the time from first diagnostic irradiation to detection of regression ranged from 5 days to 2 months. Five patients were treated with steroids, and 7 patients underwent surgeries, including ventriculoperitoneal shunt, external ventricular drainage, endoscopic third ventriculostomy, resection of vermian lesion, reservoir placement, and surgical biopsy. An episode of regression followed by regrowth occurred in 3 cases. Four hypotheses were proposed, including radiation exposure, surgical procedures, effects of steroids, and immune reaction triggered by intervention, which are detailed in Table 1.

DISCUSSION

Spontaneous regression is an exceptional phenomenon that has been reported in various malignant tumors with an estimated incidence of 1 in 60,000–100,000 patients.[11] It is documented as a rare phenomenon in testicular GCTs; these tumors were termed burned-out testicular tumors in 1955 by Slater et al.[12] In testicular GCTs, spontaneous regression most frequently occurred in patients with seminomas and was occasionally reported in yolk sac tumors and embryonic carcinomas. Teratomas are considered to be resistant to regression.[13] With regard to intracranial GCTs, the phenomenon of tumor regression is extremely rare with only 10 cases (including the present case) reported (Table 1).[2-10] Germinoma was diagnosed in 9 cases, whereas only 1 case reported by Mascalchi et al.[9] was considered to be embryonal carcinoma. There were 9 male patients and 1 female patient with a mean age of 22.1 ± 10.3 years (range, 12–43 years). The age of onset in these patients was relatively high, as common intracranial GCTs predominantly occur in children and adolescents. All cases demonstrated typical clinical and radiologic features of intracranial GCTs, and the tumor markers examined in previous reports all were in normal range.

The natural history of tumor regression in intracranial germinomas remains unclear, which is possibly due to the favorable response to radiation therapy. Four cases including the present case involved an episode of regression followed by regrowth,[6,9,10] which implied that the tumor regression might be irrelevant to the progression of this disease and could not be considered the same as cure. Nevertheless, all the reported cases received various interventions before regression, and we speculated that the so-called spontaneous regression might be an iatrogenic transient consequence caused by medical interventions rather than a spontaneous phenomenon. The exact mechanism of tumor regression in intracranial GCTs remains unclear. According to the reported cases, 4 hypotheses may be considered, including radiation exposure, surgical procedures, effects of steroids, and immune reaction triggered by interventions.

Radiation Exposure

Radiation exposure was discussed as a possible reason for tumor regression of intracranial GCTs. It is well acknowledged that intracranial GCTs, especially pure germinomas, are highly radiosensitive, and radiotherapy at a single dose of 11 Gy or 10 Gy in 5 fractions could achieve significant tumor shrinkage.[14] All the reported cases in this series had received diagnostic irradiation before tumor regression, including repeated CT scans and angiography. Among these cases, the time from the first diagnostic irradiation to detection of regression ranged from 5 days to 2 months. Therefore, Yoneoka et al.,[5] Ono et al.,[4] and Woo et al.[10] attributed the tumor regression of intracranial germinomas to radiation exposure. However, the radiation dosage of a single CT scan is considered to be <0.05 Gy. Even for the patient reported by Murai et al.,[2] 6 CT scans would generate radiation of <0.3 Gy; moreover, in most reported cases, only 1 CT scan was performed. Therefore, such a small dosage of radiation would be insufficient to cause tumor regression.

Surgical Procedure

Some authors suggested the surgical procedure as causative for tumor regression. Everson and Cole[15] reviewed the literature on 176 cases of spontaneous regression of various malignant tumors and showed that 40% of these patients underwent surgical procedures before the regression. It is considered that surgical procedures could influence the immunologic status of the patient and lead to local inflammatory response, such as lymphocytic infiltration, which might introduce an inflammatory antitumor response and cause tumor regression.[16] The case reported by Ide et al.[6] involved a suprasellar germinoma that manifested with transient regression after placement of a ventriculoperitoneal shunt, and Fujimaki et al.[3] reported a case of multiple intracranial germinomas in which a pineal lesion regressed after resection of the cerebellar germinoma. However, there are 3 cases in this series in which no surgical procedures were performed, which suggests that the hypothesis of surgical trauma is inconclusive.

Steroids

Effects of steroids have also been proposed to be a cause of tumor regression of intracranial GCTs. Steroids, owing to their lymphocytotoxic properties, have been widely used for treatment of leukemia for >60 years.[17] Masoudi et al.[7] reported spontaneous regression of a large pineal germinoma that showed a significant reduction in tumor size (almost 92%) after 14 days of dexamethasone administration. Intracranial germinomas are pathologically characterized by the presence of tumor-infiltrating lymphocytes, and administration of steroids could change the total immunologic defense mechanism of the patients, enabling elimination of the germinomas. Therefore, some authors assumed that steroids might contribute to the regression of intracranial germinomas via lympholytic effects.[7-9] However, a clinical study of 153 patients with intracranial GCTs showed no tumor regression, despite the fact that all the patients received steroids perioperatively.[18] Furthermore, in 4 reported cases in this series, treatment with steroids was not administered, which challenged the hypothesis of steroid-induced tumor regression.

Immune Reaction Triggered by Interventions

Intracranial germinomas are pathologically characterized by the presence of tumor-infiltrating lymphocytes, which could be influenced by medical interventions, including administration of steroids and surgical procedures. Murai et al.[2] postulated that surgical procedures transiently suppressed the immune host response, and the following rebound reaction during the postoperative recovery phase led to germinoma regression. In the present case, no surgical procedure was performed before tumor regression; moreover, radiation exposure of a single CT scan was insufficient to cause tumor regression. Furthermore, a short course of steroids seemed unlikely to cause the tumor regression. Based on the literature, we considered the monophyletic theory might be insufficient to explain the spontaneous regression of this disease. As revealed by a recent study,[19] tumor-infiltrating lymphocytes in germinomas have dual roles in both suppressing and promoting germinoma cell growth. The complex interplay between lymphocytes and germinoma cells could be easily influenced by radiation exposure, surgical procedures, or administration of steroids. Therefore, we believed the tumor regression in intracranial germinomas might be caused by complex immune reactions triggered by medical interventions.

CONCLUSIONS

Although 4 hypotheses, including radiation exposure, surgical procedures, effects of steroids, and immune reaction triggered by intervention, were proposed, the mechanism of spontaneous regression in intracranial GCTs is still equivocal. We speculated that it might be an iatrogenic transient phenomenon caused by complex immune reactions triggered by interventions; therefore, it is necessary to be aware of the possible effect of diagnostic irradiation, surgical procedures, and steroids that may cause intracranial GCT regression, especially for patients with symptomatic improvement, and new imaging should be recommended before further treatment. Additionally, as the tumor regression in these cases could be readily triggered by medical interventions, an immunologic approach might be a promising modality for future investigation of intracranial GCTs, which might avoid unnecessary external ventricular drainage or ventriculoperitoneal shunt and their potential complications.

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