

## Case Report

## Primary human chorionic gonadotropin secreting germinoma of the corpus callosum

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**Abstract****Background:** Primary intracranial germinomas are a rare subset of intracranial tumors derived from mis-incorporated germ cells within the folding neural plate during embryogenesis. Though known to arise from midline structures in the central nervous system (CNS), occurrence within the corpus callosum is exceedingly rare.**Case Description:** We present a rare case of secreting primary intracranial germinoma with extensive intraventricular metastasis presenting as a multi-cystic butterfly lesion in the genu of the corpus callosum in a young boy.**Conclusion:** Intracranial germ cell tumors must be considered for any multi-cystic lesion arising from midline structures in the CNS in the preadult population.**Key Words:** Corpus callosum, germinoma, intracranial, secreting**Access this article online****Website:**[www.surgicalneurologyint.com](http://www.surgicalneurologyint.com)**DOI:**

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**Quick Response Code:****INTRODUCTION**

Primary intracranial germinomas are an extremely rare subset of germ cell tumors (GCT) that arise primarily from midline structures in the central nervous system (CNS). Intracranial germinomas account for 0.5-2.0% of all intracranial tumors<sup>[24]</sup> and 50-60% of CNS GCT.<sup>[15,17]</sup> The two locations where these tumors are most commonly found are the pineal region and the suprasellar region.<sup>[15]</sup> Other less common regions where these tumors have been found include the basal ganglia, the thalami,<sup>[20]</sup> the corona radiata,<sup>[12]</sup> temporal lobe,<sup>[25]</sup> cerebellopontine angle,<sup>[8]</sup> medulla oblongata,<sup>[25]</sup> and intramedullary spinal cord.<sup>[14]</sup> A proposed explanation for

the location of these tumors in midline structures of the CNS is the mis-incorporation of primordial germ cells into the cranially migrating intraembryonic mesoderm during the formation of the primitive streak in the third week of embryogenesis. These germ cells commonly arise from structures lying laterally adjacent to the embryonic disc, such as the trophoblastic layer, amnion, and yolk sac endoderm. During the subsequent folding of the neural plate into the neural tube, these cells are mistakenly enfolded and incorporated into the CNS, where they may give rise to GCT in future.<sup>[9,18-20]</sup>

We present a rare case of primary intracranial GCT arising from the corpus callosum in a 15-year-old child treated at our institution.

## CASE REPORT

### History

A 15-year-old Malay boy with no significant past medical history was referred to our institution with a 2-month history of intermittent fever, recurrent headaches, vomiting, significant weight loss, and deterioration in school performance. He did not have any significant drug, family, or developmental history.

### Physical examination

On examination, he was found to be disorientated to time, place, and person. He also demonstrated terminal past-pointing bilaterally and left-sided dysidiadochokinesia.

### Investigations

Initial blood investigations revealed a white blood cell count of  $6.92 \times 10^9/L$  and a C-reactive protein level of  $<5.0$  mg/L. Serum alphafetoprotein (AFP) and human chorionic gonadotropin (b-HCG) were not elevated. Other abnormal serum biochemical parameters included free thyroxine (FT4) of 9.4 pmol/L, thyroid stimulating hormone (TSH) of 3.92 mIU/L, follicular stimulating hormone of  $<0.1$  IU/L, luteinizing hormone of  $<0.07$  IU/L, sodium of 155 mmol/L and serum osmolality of 323 mOSm/kg. Cerebrospinal fluid (CSF) AFP levels were normal but CSF b-HCG levels, however, were markedly elevated at 1837.01 IU/L. Contrast computer tomographic (CT) imaging revealed a heterogenous 4 cm mass centered in the genu of the corpus callosum, filling the anterior aspect of the third ventricle and spreading along the margins of both frontal horns, causing obstruction of the Foramina of Monro and hydrocephalus. Thickening and enhancement was also noted along the margins of both lateral ventricles and a  $1.3 \times 0.9$  cm enhancing nodule visualised in the 4<sup>th</sup> ventricle [Figure 1]. Further workup also revealed that the patient was suffering from central diabetes insipidus as well as panhypopituitarism. After neurosurgical

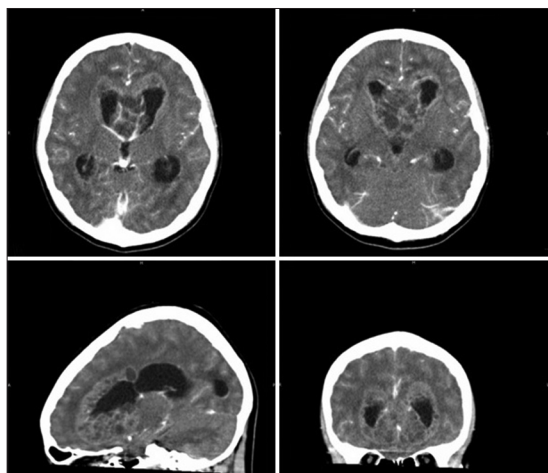
team review, the diagnosis of GCT with extensive intraventricular CSF seeding was considered. Subsequent magnetic resonance imaging (MRI) brain reported multiple intraventricular contiguous and noncontiguous cystic masses with extension superiorly into the frontal horns, the genu of the corpus callosum and the septum pellucidum, inferiorly into the suprasellar region, as well as laterally into the right temporal horn [Figure 2]. Small cystic foci were also noted in the vicinity of the pineal gland. MRI attempted at this juncture was not augmented with contrasted medium due to acute kidney injury from excessive diuresis precipitated by central diabetes insipidus. No spinal drop metastases were visualized on MRI.

### Pathological findings

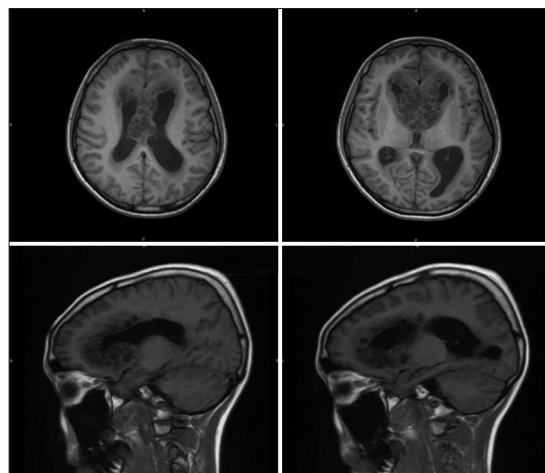
The patient underwent open craniotomy and biopsy of the intraventricular portion of the tumor. Histology revealed a germinoma composed of sheets of large primitive cells with round nuclei bearing prominent nucleoli, and ample clear cytoplasm with discrete cell membranes, interrupted by fibrous septa containing smaller reactive lymphocytes [Figure 3]. Immunohistochemical staining showed positive reactivity for CD117 (c-kit) and placental alkaline phosphatase, confirming the diagnosis of germinoma. Although CSF b-HCG was found to be elevated at 1837.01 IU/L, immunohistochemical staining for the same was negative.

### Postoperative course

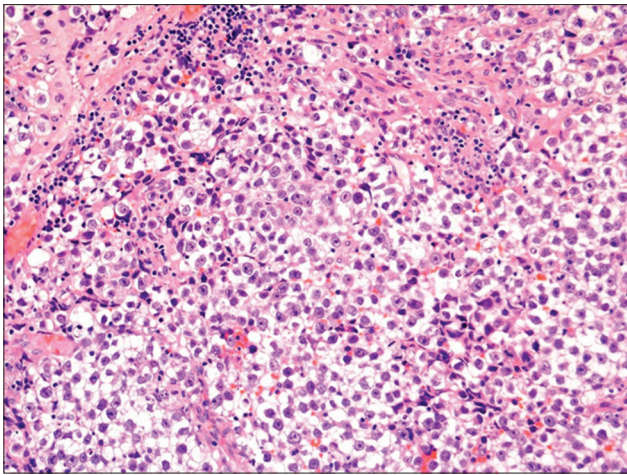
The patient underwent four cycles of carboplatin, etoposide, and ifosfamide as per International Society of Pediatric Oncology Central Nervous System Germ Cell Tumor (SIOP CNS GCT) 96 protocol and subsequent craniospinal irradiation (CSI) of 54 Gray (Gy) in 32 fractions, which he tolerated well. Radiologically, his lesions remained stable despite completing treatment [Figure 4] but he demonstrated good biochemical response with CSF b-HCG falling from



**Figure 1: Contrast CT of tumor in corpus callosum with intraventricular involvement**



**Figure 2: Noncontrast MRI of tumor in corpus callosum with intraventricular involvement**



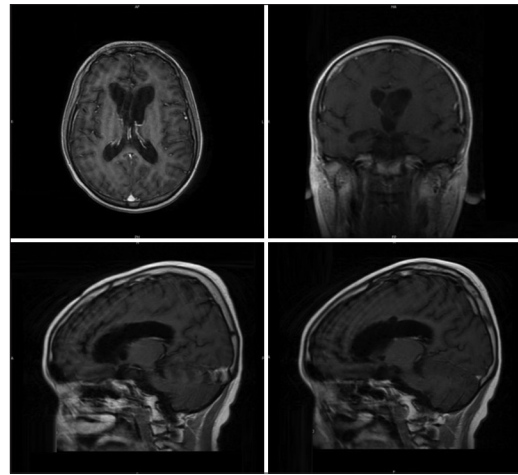
**Figure 3: Photomicrograph of germinoma (H and E, ×200) featuring sheets of large primitive cells with round nuclei bearing prominent nucleoli, and ample clear cytoplasm with discrete cell membranes, interrupted by fibrous septa containing smaller reactive lymphocytes**

1837.01 IU/L to less than 2.0 IU/L. The patient had to be on permanent hormonal replacement therapy for panhypopituitarism. His last CSF b-HCG reading taken 12 months after completion of treatment remains stable at <1.2 IU/L and most recent MRI brain done 15 months after completion of treatment shows no evidence of recurrence.

## DISCUSSION

Lesions of the corpus callosum are often mentioned in association with aggressively infiltrative tumors such as glioblastoma multiforme (GBM) or demyelinating diseases such as multiple sclerosis.<sup>[2]</sup> The occurrence of primary CNS GCT in the corpus callosum is extremely rare and oftentimes not considered among other preoperative differential diagnoses. GCT are largely a disease of the preadult age group, with majority of afflicted patients no older than the age of 20.<sup>[5,15,26]</sup> On CT imaging, a proportion (19%) of these tumors may show calcification.<sup>[13]</sup> On MRI, these tumors may demonstrate the following: Hypointensity to isointensity on T1-weighted MRI, hyperintensity to isointensity on T2-weighted MRI, homogenous enhancement with gadolinium contrast on MRI, and a multi-cystic appearance.<sup>[5,13]</sup> The presence of a multi-cystic tumor in a midline location in an adolescent should therefore always raise the suspicion of a GCT; the significance being that these tumors have a relatively better prognosis than most other malignant brain tumors and are readily treatable with chemotherapy and radiation, hence averting morbid surgery.

As the genu of the corpus callosum constitutes the roof of the frontal horns, tumor spread along the CSF pathways probably accounts for the extent of intraventricular



**Figure 4: Contrasted MRI 1 month after completion of treatment**

dissemination seen in this patient. Tumors of the corpus callosum are known to have progressed extensively before the manifestation of symptoms due to their location's relatively noneloquent nature.<sup>[25]</sup>

Raised CSF b-HCG levels coupled with histological confirmation of germinoma suggest the following differential diagnoses: (1) germinoma with syncytiotrophoblastic giant cells (STGC), (2) HCG-secreting germinoma, or (3) mixed GCT with both germinomatous and nongerminomatous components. The latter is especially in the light of a markedly raised tumor markers (b-HCG) as described in our case report.<sup>[5,29]</sup> Tumor marker levels in non-germinomatous germ cell tumors (NGGCT) tend to be higher, but to date, there is no definitive cut-off value that distinguishes germinoma from NGGCT, although it is commonly quoted that germinomas secrete b-HCG only up to levels of 50.0 IU/L. Cases of germinomas secreting very high levels of b-HCG have been documented,<sup>[5,7]</sup> complicating distinction between the former and NGGCT. No STGC were identified in our patient's specimen even after detailed histological examination and B-HCG immunohistochemical staining performed was negative. It is possible that any STGC or nongerminomatous component could have been missed on biopsy of the tumor. Any difference in prognosis between HCG-secreting germinoma and germinoma with STGC remains unclear to date.<sup>[10,21]</sup> Nevertheless, secreting germinomas and NGGCT tend to be less responsive than nonsecreting or 'pure' germinomas to treatment, hence portending a poorer prognosis.<sup>[6]</sup> HCG-secreting germinomas have demonstrated significantly worse outcomes vis-a-vis their nonsecreting counterparts when treated with both chemotherapy and radiation<sup>[1]</sup> as well as with radiation-alone.<sup>[6]</sup>

Treatment outcomes comparable with that of unifocal germinomas has been shown to be possible for initially disseminated intracranial germinomas (IDIG). A small single-institution series showed excellent outcomes

**Table 1: Reported cases of primary intracranial germ cell tumors in corpus callosum**

Case No	Author (Year)	Age (years)/sex	Histology	Associated lesions	Size (mm)	Initial symptom
1	Carrillo <i>et al.</i> (1977) <sup>[4]</sup>	13/M	Embryonal carcinoma	Me; pineal (mature teratoma)	NM	Raised intracranial pressure
2	So and Ho (1980) <sup>[22]</sup>	26/M	Germinoma	S; thalamus, cerebral peduncle	40	Involuntary movements
3	Liang <i>et al.</i> (2002) <sup>[13]</sup>	20/M	Immature teratoma/germinoma	S; Frontal white matter, spinal dissemination	NM	NM
4	Utsuki <i>et al.</i> (2005) <sup>[25]</sup>	22/M	Germinoma	NM	62	Memory disturbance and untidy behavior
5	Utsuki <i>et al.</i> (2005) <sup>[25]</sup>	28/M	Germinoma	NM	78	Right lower limb weakness and memory disturbance
6	Sugiyama <i>et al.</i> (2006) <sup>[23]</sup>	8/M	Germinoma	S; Basal ganglia, internal capsule	30	Precocious puberty
7	Voirin <i>et al.</i> (2008) <sup>[27]</sup>	<18/NM	NM	NM	NM	NM
8	Kamoshima <i>et al.</i> (2008) <sup>[11]</sup>	31/M	Mature teratoma	Me; pineal (germinoma)	10	Anorexia nervosa
9	Yonezawa <i>et al.</i> (2010) <sup>[29]</sup>	31/M	Germinoma	None	40	Speech disturbance and right hand numbness
10	Present case	15/M	Germinoma	S; intra-ventricular dissemination	40	Deteriorating school performance

Me: Metachronous lesions, NM: No mention; S: Synchronous lesions, M: Male

for IDIG treated with intensive platinum-based chemotherapy combined with CSI (median dose 30.0 Gy; range 21.0-36.0 Gy) and focal boosts to both primary and secondary lesions (median dose 30.6 Gy; range 30.6-55.0 Gy) with minimal long-term side effects.<sup>[5]</sup> This study highlighted the possibility of achieving disease outcomes similar to unifocal lesions in the IDIG group with appropriate treatment. The SIOP CNS GCT 96 trial, in contrast, revealed that treatment with CSI (24.0 Gy) with tumor bed boost (additional 16.0 Gy) alone in the IDIG group achieved excellent outcomes with 5 year overall survival (OS) and event-free survival (EFS) of 98% and that the addition of platinum-based chemotherapy to radiation conferred no additional survival benefit.<sup>[3]</sup> These findings suggest that radiation should be the key treatment modality in IDIG but definitive consensus on the optimum treatment for this group requires further confirmation with more clinical trials.

Remnant lesions are risk factors for recurrence in most pediatric cancers but appear not to be in the case of germinoma. The appearance of a residual lesion after completion of treatment with chemotherapy suggests the possibility of remnant fibrosis/necrosis or a residual nongerminomatous component that was missed on histological sampling in the first place, the most significant of which is a mature teratomatous component. A distinct phenomenon known as the 'growing teratoma syndrome' in which the tumor mass is seen to enlarge during or after chemotherapy in the presence of falling serum markers has been reported.<sup>[16]</sup> This is not to be confused with disease recurrence as the treatment for teratoma is surgical excision while that of recurrent germinoma is further chemotherapy and/or irradiation. There has been renewed interest in the role of relook surgery to assess residual lesions, especially in the setting

of normalization of serum/CSF tumor markers given the likelihood of a residual teratomatous component.<sup>[6]</sup>

## CONCLUSION

Intracranial GCT must be considered for a multi-cystic lesion arising from midline structures in the CNS in the preadult population. Histological sampling must be interpreted in the context of serum/CSF biochemical markers to achieve accurate diagnosis. Treatment outcomes of IDIG are excellent if appropriate therapy can be administered.

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