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# Cystic Trophoblastic Tumor in a Primary Central Nervous System Post-Chemotherapy Germ Cell Tumor: The First Case Report

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## Abstract

Cystic trophoblastic tumor (CTT) is an uncommon trophoblastic proliferation of germ cell tumor origin, mostly reported in post-chemotherapy metastases of testicular germ cell tumors and rarely primary untreated testicular tumors. To date, we are not aware of occurrence in a non-testicular tumor. A 12-year-old boy presented with limb swelling, increased appetite, weight gain, and precocious puberty. Evaluation revealed right frontal lobe mass and elevated  $\alpha$ -fetoprotein and  $\beta$ -human chorionic gonadotrophin. After response to neoadjuvant chemotherapy, the tumor was resected. Microscopically, the resection contained predominantly smooth muscle tissue with scattered small foci of glandular teratoma and CTT. Immunohistochemistry (SALL4, glypican 3) revealed no residual yolk sac tumor. Fluorescence in situ hybridization revealed gain of chromosome 12p. The patient has been disease-free for 13 years. This report expands the spectrum of primary central nervous system germ cell tumors with the occurrence of CTT in this site.

## Keywords

germ cell tumor, cystic trophoblastic tumor, choriocarcinoma, yolk sac tumor

## Introduction

Cystic trophoblastic tumor (CTT) was first described by Ulbright et al in post-chemotherapy retroperitoneal lymph node dissection specimens from patients with metastatic nonseminomatous germ cell tumors.<sup>1</sup> Subsequently, less than a hundred such cases have been described in the literature, mostly in post-chemotherapy specimens, and rarely in primary untreated testicular tumors.<sup>2</sup> One of the proposed hypotheses for the pathogenesis of this lesion is that it represents regression of choriocarcinoma. To our knowledge, CTT has not been described in an extragonadal germ cell tumor. A minority occur in primary chemotherapy-naïve testicular tumors.<sup>1,3</sup> Despite being a trophoblastic neoplasm that often is found in post-chemotherapy metastases, the behavior of these metastatic lesions has been associated with good prognosis, approximating that of teratoma.<sup>3</sup> We report the development of CTT in a primary central nervous system germ cell tumor, which has not been previously described.

## Materials and Methods

Four-micrometer-thick sections were prepared from the specimen for hematoxylin and eosin staining and

immunohistochemistry. Immunohistochemical staining was performed in an automated instrument (Dako) with antibodies directed against GATA3, SALL4, and glypican 3. Fluorescence in situ hybridization (FISH) was performed on formalin-fixed, paraffin-embedded sections, using methods previously described.<sup>3</sup>

## Results

A 12-year-old boy presented with limb swelling, increased appetite, weight gain, precocious puberty, headache, and vomiting. Subsequent evaluation with computed

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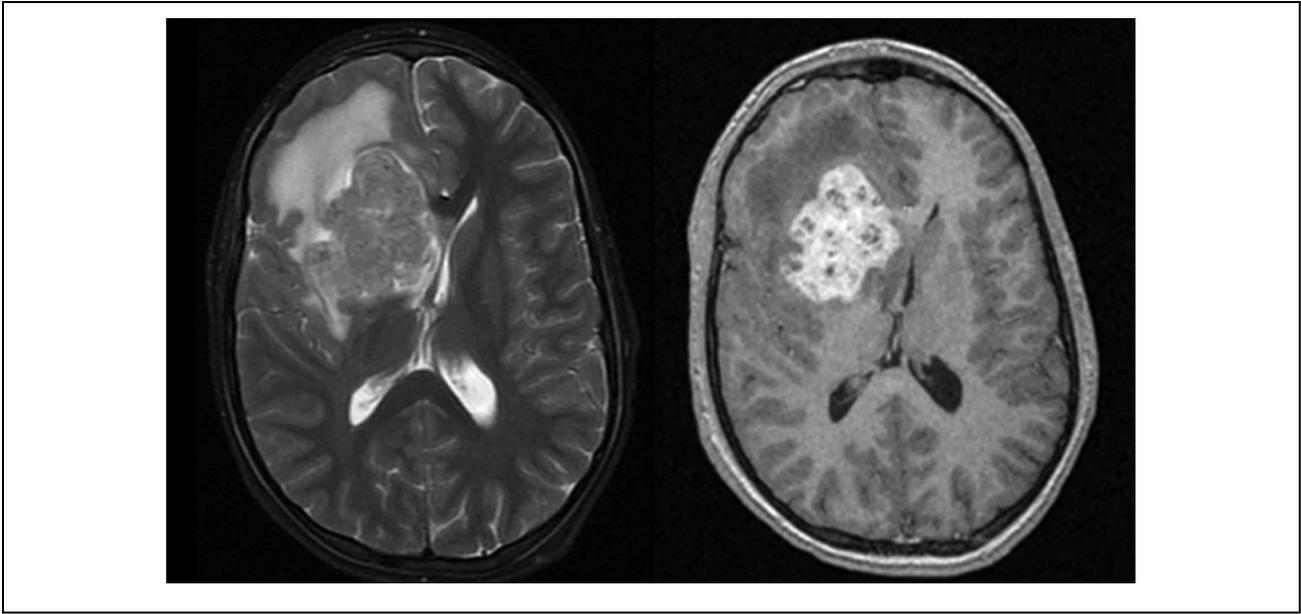
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**Figure 1.** Magnetic resonance imaging pre-treatment shows a heterogeneous, intermediate signal mass, which is isointense to gray matter in the axial T2 image (left). The axial post-gadolinium image (right) shows avid enhancement.

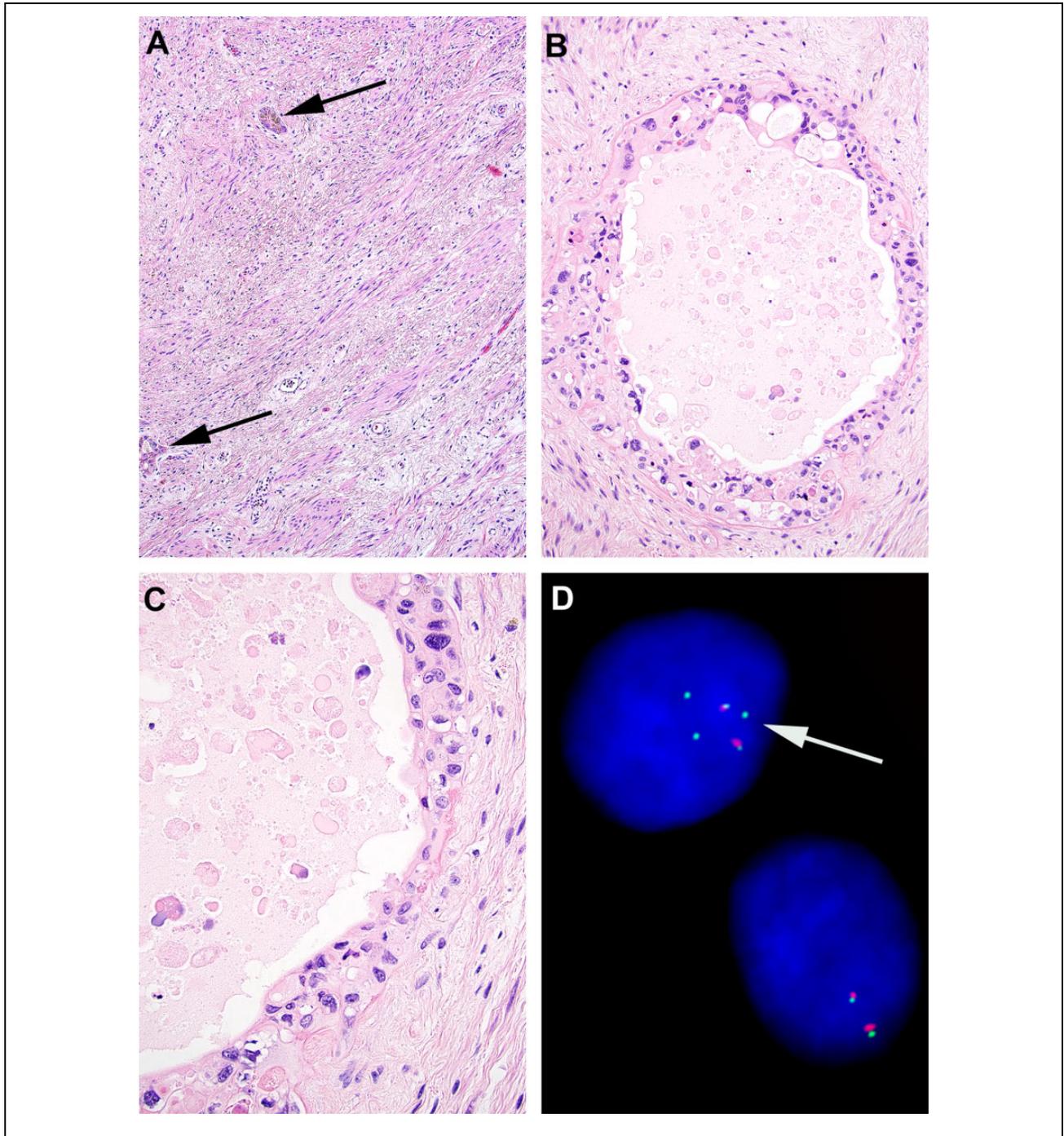
tomography and magnetic resonance imaging (MRI) revealed a 5-cm right frontal lobe mass (Figure 1). Serum  $\alpha$ -fetoprotein (AFP; 2939 IU/mL) and  $\beta$ -human chorionic gonadotrophin (hCG; 15 522 IU/mL) were elevated. After good response to 6 cycles of neoadjuvant carboplatin, etoposide, and ifosfamide, the tumor was resected. Two cycles of adjuvant chemotherapy, and 54 Gy of adjuvant proton beam radiation to the craniospinal and right frontal areas were administered. The patient has been disease-free during follow-up studies with hCG and AFP at 13 years after primary treatment.

At gross examination, the resected tissue showed a tan gray, lobulated, firm appearance. On cut surface, the lesion was slightly whorled and consisted of lobulated tan tissue with focal red-black, pinpoint, hemorrhagic foci in cysts. Histologically, the lesion was composed of predominantly smooth muscle, punctuated by minute foci of glandular and cystic trophoblastic elements (Figure 2A-C). The lining of the cystic spaces was composed of cells with a trophoblastic appearance, including multinucleated cells with smudged-appearing nuclei, and central eosinophilic fibrinoid material. The biphasic pattern of choriocarcinoma was not present, nor was there necrosis or hemorrhage. No definite yolk sac tumor was appreciable. Immunohistochemical staining revealed negative SALL4 and glypican 3, arguing against residual yolk sac tumor. GATA3 was negative; however, the CTT foci were not well visualized in the additional sections for immunohistochemistry. FISH revealed gain of material from chromosome 12p (but not isochromosome 12p; Figure 2D).

## Discussion

Cystic trophoblastic tumor is a likely under-recognized entity in germ cell tumor classification with disputed pathogenesis. Its true incidence is not entirely known, due to the relative rarity of testicular cancer compared with other cancers, and potentially underrecognition. One hypothesis is that this represents a regressing choriocarcinoma, with stepwise degeneration of solid to cystic component as the more aggressive cells are eliminated by chemotherapy or spontaneous regression. This leads to the persistence of a slow growing, less aggressive component of intermediate-type trophoblastic cells that develop into CTT.<sup>3</sup>

Morphologically, CTT may consist of solid foci or small clusters of modestly pleomorphic trophoblastic cells, and variably sized, degenerative appearing cysts, typically measuring <3 mm with circumscribed borders. Cysts are lined by trophoblast cells with abundant, eosinophilic cytoplasm that vary from a single cell layer to several in thickness, forming intracystic papillary tufts or cribriform arrangements. Most of the lining cells are mononucleated and many have a “smudged” chromatin pattern, although occasional multinucleated cells occur, sometimes with cytoplasmic lacunae. Many of the lining cells have a squamoid appearance, although no extracellular keratin production is apparent. Mitotic activity is inconspicuous, with only rare mitotic figures identified.<sup>1,2</sup> In general, cystic trophoblastic elements would have a differential diagnosis that includes somatic malignancy, especially squamous cell carcinoma, trophoblastic



**Figure 2.** (A) Histologic examination of the post-treatment resection showed predominantly smooth muscle tissue punctuated by minute teratomatous glands (arrows). (B) Rare cystic trophoblastic elements were noted, forming cystic structures lined by cells of varying sizes. (C) Higher magnification of the trophoblastic lining shows multilayering of cells with variable nuclear size and larger nuclei showing a smudged appearance of the chromatin. (D) Fluorescence in situ hybridization evaluation shows multiple copies of the 12p probe (green, arrow), compared with the centromere (red).

differentiation including epithelioid trophoblastic tumor, placental site trophoblastic tumor, or unclassified trophoblastic tumor. These can be excluded by careful histologic examination and immunohistochemistry. Squamous cell

carcinoma would be negative for hCG and inhibin, and importantly, one should not diagnose a secondary somatic malignancy of germ cell tumor origin unless there is overgrowth of a single element more than an entire 4× field (5

mm diameter), which is rarely the case with CTT. Epithelioid trophoblastic tumor usually forms cohesive nests of squamoid cells with abundant cytoplasm and mostly single, pleomorphic, and hyperchromatic nuclei with variable prominent nuclei. Choriocarcinoma can be excluded by absence of the biphasic pattern of cytotrophoblastic and syncytiotrophoblastic cells with associated hemorrhage or necrosis.

Cystic trophoblastic tumor is known for its low malignant potential, noninfiltrative pattern, and low mitotic index.<sup>3</sup> Current thinking is that the prognosis comparable to residual teratoma and that patients usually do not require additional chemotherapy.<sup>4</sup> Germ cell tumors other than teratoma in patients who had chemotherapy are associated with recurrence and typically considered to require additional chemotherapy.<sup>5,6</sup> FISH studies in the current case revealed gain of chromosome 12p, although not isochromosome 12p, which is a molecular alteration that has been described in both testicular and primary nervous system germ cell tumors.<sup>7</sup>

In this report, we describe, to our knowledge, the first example of CTT in a central nervous system germ cell tumor, occurring in a 12-year-old boy. The patient had an excellent response to therapy and is disease-free at 13 years of follow-up, implying good prognosis, similar to CTT found in post-chemotherapy residual retroperitoneal masses in testicular germ cell tumor patients. Awareness of this entity in the nervous system expands the current knowledge of primary germ cell tumors at this site and may potentially guide adjuvant therapy.

### Authors' Note

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### Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

### Informed Consent

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### Trial Registration

Not applicable, because this article does not contain any clinical trials.

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