Misdiagnosis of elevation of $\beta$-hCG in cystic craniopharyngioma: illustrative case

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BACKGROUND  Craniopharyngiomas and germ cell tumors (GCTs) are both rare intracranial tumors commonly present in childhood or middle age. They share similar clinical and radiological features. GCTs commonly give rise to tumor markers in the cerebrospinal fluid, hence guiding the treatment plan.

OBSERVATIONS  This article reports the case of a 5-year-old boy with a large sellar and suprasellar mass with obstructive hydrocephalus. Laboratory studies showed increased beta-human chorionic gonadotrophin ($\beta$-hCG) levels in the cystic fluid, suggestive of choriocarcinoma. He underwent 3 cycles of chemotherapy but showed a poor response. Further aspiration followed by tumor debulking was performed, and histopathological examination revealed craniopharyngioma.

LESSONS  This case report indicates that $\beta$-hCG, commonly regarded as a specific tumor marker for choriocarcinoma, is detectable in other forms of suprasellar tumors. The authors highlight clinical and radiological features of suprasellar tumors that can be misdiagnosed as intracranial GCTs. The relevance of tumor markers and indications for histopathological confirmation are discussed.

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KEYWORDS  craniopharyngioma; intracranial germ cell tumor; tumor marker; beta-human chorionic gonadotrophin; $\beta$-hCG; oncology

Craniopharyngioma is the most common nonglial intracranial pediatric tumor derived from cellular remnants of Rathke's pouch.\(^1\)–\(^4\) Craniopharyngioma accounts for 54% of tumors in the sellar-chiasmatic region during childhood.\(^3\)–\(^5\) Although this tumor can present at any age, a bimodal age distribution shows peak incidence rates in children aged 5 to 15 years and adults aged 40 to 70 years.\(^3\)–\(^5\) Other differential diagnoses of suprasellar-sellar masses include chiasmatic-hypothalamic glioma, germinoma, Rathke's cleft cyst, hypothalamic hamartoma, arachnoid cyst, pituitary adenoma, and meningioma, with the last 2 rarely presenting in children.\(^5\)

Similar to craniopharyngiomas, intracranial germ cell tumor (ICGCT) affects the suprasellar region, leading to identical clinical manifestations. Both tumors can be manifested by visual disturbances, varying degrees of hypopituitarism, and raised intracranial pressure (ICP) symptoms.\(^3\)–\(^6\)\(^,\)\(^7\) However, diabetes insipidus, precocious puberty, anorexia, and weight loss are commonly associated with ICGCT.\(^6\)–\(^8\)

Most craniopharyngiomas are identified on the basis of clinical and neuroradiological features.\(^5\)–\(^9\) Neuroimaging is useful in distinguishing various suprasellar pathologies by allowing evaluation of cystic versus solid lesions, contents of cysts, and the infiltrative nature of tumors. ICGCT shares similar radiological features with craniopharyngiomas. Compared with teratomas, which have a combination of cystic and solid elements such as fat and bones visible on imaging,\(^6\)–\(^10\) ICGCTs are generally noncystic.\(^8\) Craniopharyngioma variously has solid, cystic, or a combination of cystic and solid elements\(^2\)–\(^4\)–\(^8\)–\(^11\) and is generally a well-circumscribed mass, with the largest part of the tumor presenting as an enormous single cyst or multilobular cysts containing cholesterol crystals.\(^2\) Calcifications have a craggy, popcorn-like appearance with fine eggshell lines\(^1\) and occur in 51% to 90% of pediatric craniopharyngiomas,\(^2\)–\(^3\)–\(^5\) providing important radiological clues for the diagnosis.

With or without gadolinium enhancement, magnetic resonance imaging (MRI) is critical in demonstrating the tumor’s relationship to the major vessels, optic chiasm, infundibulum, and hypothalamus. Nevertheless, distinctions between craniopharyngiomas and other intracranial cystic lesions can be difficult.
Illustrative Case

A 5-year-old boy presented with a 2-month history of frequent headaches, lethargy, weight loss, and vomiting, with no history of trauma or evidence of infection. He was alert and conscious, and his pupils were equal and reactive bilaterally. Computed tomography (CT) of his brain showed a large sellar and suprasellar mass causing obstructive hydrocephalus. The child underwent ventriculoperitoneal shunt placement. MRI of the brain performed 3 days after surgery showed an enhancing mixed solid-cystic mass occupying the sellar and both frontal regions. The mass was larger on the right than on the left, compressing the surrounding brain parenchyma (Fig. 1).

Given persistent raised ICP symptoms despite cerebrospinal fluid (CSF) diversion surgery 2 weeks earlier, an Ommaya shunt was inserted during image-guided surgery to decompress the cystic component of the tumor. Cystic fluid was sent for tumor markers, which revealed that beta-human chorionic gonadotrophin ($\beta$-hCG) was elevated (1418 IU/L). Serum alpha-fetoprotein ($\alpha$-FP) and $\beta$-hCG levels were obtained, both of which were within normal range. Chemotherapy was initiated upon considering the possibility of ICGCT based on the $\beta$-hCG in the cystic fluid.

The patient’s intracranial mass increased in size, particularly the cystic component, requiring intermittent Ommaya reservoir tapping to relieve symptoms. Serial cystic fluid measurements of $\beta$-hCG remained high after 3 cycles of chemotherapy, indicating the diagnosis was improbable (Fig. 2). Debulking surgery was performed (Fig. 3), and the finding of the histopathological examination was consistent with craniopharyngioma. However, the result of $\beta$-hCG staining of tissue fragments was negative (Fig. 4). Repeated CT and MRI after surgery
showed residual tumor with bilateral subdural effusion requiring drainage (Fig. 5), after which the patient then became asymptomatic.

**Discussion**

**Observations**

Diagnosis of ICGCT depends on the clinical condition of the patient and a midline intracranial tumor combined with increased levels of tumor markers such as β-hCG and αFP in the serum and CSF.6,8,12 αFP is a marker for tumors with yolk sac components, whereas β-hCG is commonly expressed by choriocarcinomas, malignant teratomas, and embryonal carcinomas containing trophoblastic tissue.4 hCG is physiologically produced by placental sycnotrophoblasts of the placenta to maintain pregnancy.5,6 Although it is not a specific placental hormone and can be found in trophoblast-derived lesions present in germinoma tissue,5,6,9 High levels of hCG essentially confirm the diagnosis of ICGCT; hence, tumor markers have occasionally been used independently for patient management.5,6,8,9,13 Thus obviating the need for invasive sampling and complications during neurosurgical procedures.2,6,8,9

The specificity of β-hCG as a marker for ICGCT has been questioned because there are certain risks in accepting low elevations of β-hCG alone in serum and/or CSF, which can be encountered in other pathologies, such as pituitary adenoma, craniopharyngioma, and arachnoid cysts.5,9,14 Regarding clinical relevance, elevated β-hCG in CSF is not a specific marker for ICGCT because cystic fluid may have leaked into the ventricular system, causing a false-positive result.

Tumor markers in serum and CSF should not have the same cutoff values.15,16 Hu and colleagues successfully determined β-hCG diagnostic cutoff points of CSF β-hCG ≥8.2 IU/L and serum β-hCG ≥2.5 IU/L and empirically adjusted the criteria for αFP to ≥3.8 ng/mL in CSF and to ≥25 ng/mL in serum.15 These evidence-based criteria of β-hCG and αFP increased diagnostic sensitivity for ICGCTs, helping early and formal diagnosis.

Harris and colleagues measured β-hCG levels in the plasma, CSF, and cystic fluid of 9 patients with biopsy-proven typical craniopharyngiomas.17 Plasma and CSF β-hCG levels were undetectable (<15 IU/L) in 8 patients, although all patients had raised levels of β-hCG in craniopharyngioma cystic fluid.17 A similar study conducted by Honegger and colleagues suggested that markedly elevated hCG values in cystic fluid (>300 IU/L for total hCG immunoactivity) indicate craniopharyngioma. In both studies, half of the subjects showed positive immunostaining for hCG.9,17 The hCG-positive cell clusters were focally present in small numbers below the epithelial surface of the stroma.17 It is possible that they are present in all tumors but not demonstrable because of sampling issues.17
Cranioopharyngioma cases with high CSF tumor markers ($\beta$-hCG, aFP) are rare in the worldwide literature, although a similar case was published by Moschovi and colleagues, who described a 14-month-old girl with a suprasellar cystic and partially solid mass treated as a GCT on the basis of a raised serum level of aFP.\textsuperscript{1} Subtotal tumor excision was performed given a poor response to chemotherapy, and findings were consistent with cranioopharyngioma.\textsuperscript{1} Nada and colleagues reported a case of a 15-year-old boy with a large suprasellar and retrostellar mass in whom the first surgical specimen was reported as a cranioopharyngioma.\textsuperscript{12} In a second histological examination, the tumor was found to be a nongerminomatous GCT and positive for aFP.\textsuperscript{13} This supports the GCT family theory set forth by Plowman and colleagues that cranioopharyngioma and GCT present 2 sides of the same entity, although a wide variety of tumors with variable secretion of tumor markers may exist between them.\textsuperscript{7}

Karavitaki and colleagues found 2 collision lesions: a gonadotrophic adenoma with adamantinomatous cranioopharyngioma and a corticotrophic adenoma with Rathke’s cleft cyst.\textsuperscript{4} It is possible that cranioopharyngioma can coexist with other pathologies, in keeping with dysembryogenesis.\textsuperscript{4}

In cases in which tumor markers do not correlate with radiological findings and diagnosis is uncertain, histological confirmation serves as a better standard of care.\textsuperscript{6,10,12,14} Exceptions can be made in patients with multifocal midline (pineal/suprasellar) tumors because a majority harbor pure germinoma.\textsuperscript{14} As far as we know, no prior studies concerning $\beta$-hCG level in cystic fluid for ICGCT have been published, owing to its rarity.

In our case, tumor samples confirmed cranioopharyngioma. Despite detailed histological examination, none of the samples demonstrated evidence of GCT tissue. $\beta$-hCG expression was not detected in the histological tumor sample, possibly due to inadequate sample size for staining.

**Lessons**

Measurements of tumor markers in serum, CSF, and cystic fluid are helpful in determining a diagnosis of intracranial cystic tumors, although absolute differentiation is not possible. Marked elevations of cystic fluid $\beta$-hCG (>300 IU/L) are suggestive of cranioopharyngioma. In cases in which elevated tumor markers are found in predominantly cystic intracranial lesions, histopathological examination of tumor tissue should be done before adjuvant treatment such as chemotherapy or radiotherapy. There is a need to continue the search for more sensitive and specific tumor markers with careful clinical evaluation of those measures to prevent misdiagnosis.

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**Disclosures**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**Author Contributions**

Conception and design: Saleh, Lim. Acquisition of data: Saleh, Ismail. Analysis and interpretation of data: Saleh, Ismail. Drafting the article: Saleh, Lim. Critically revising the article: all authors. Reviewed submitted version of manuscript: Saleh, Lim. Approved the final version of the manuscript on behalf of all authors: Saleh. Statistical analysis: Saleh. Administrative/technical/material support: Saleh. Study supervision: Ismail.

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