The Pursuit of True hCG: A Rare Intracranial Germ Cell Tumor Case

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CASE DESCRIPTION

A previously healthy 8-year-old female presented to our clinic with a multiyear history of nocturnal enuresis and urinary frequency. Patient history was significant for an overseas evaluation that involved a 3-week hospitalization where diagnostic imaging via brain magnetic resonance imaging revealed significant thickening of the pituitary stalk and gland. Further laboratory and radiographic workup revealed arginine vasopressin deficiency and growth hormone (GH) deficiency and ultimately favored isolated pituitary Langerhans cell histiocytosis as the underlying etiology due to lack of sufficient biochemical or radiographic evidence of malignancy. Serum and cerebrospinal fluid germ cell tumor markers, alpha-fetoprotein and human chorionic gonadotropin (hCG) were within the reference intervals. Pharmacologic GH stimulation testing was conducted with arginine and clonidine and both results produced peak GH levels consistent with an impaired GH reserve. The patient was started on desmopressin for arginine vasopressin deficiency, and treatment for Langerhans cell histiocytosis was not initiated.

Upon patient presentation to our hospital with persistent urinary symptoms and enuresis 3 months later and given the high index of suspicion for a germ cell tumor, an extensive evaluation was repeated. This workup, which included serum and cerebrospinal fluid tumor markers, repeat magnetic resonance imaging of the neuroaxis, abdominal ultrasound, skeletal X-ray survey, and ophthalmologic exams for visual field testing, was unremarkable beyond previously identified endocrinopathies. Upon follow-up surveillance, the patient was consequently found to have a growing infiltrative mass in the pituitary gland and stalk on magnetic resonance imaging, along with increased serum and cerebrospinal fluid β-hCG and alpha-fetoprotein (Table 1), leading to a diagnosis of localized central nervous system nongerminomatous germ cell tumor. The patient had also developed further endocrine dysfunction with central adrenal insufficiency and central hypothyroidism. They underwent a multimodal treatment protocol consisting of chemotherapeutic agents including ifosfamide, carboplatin, and etoposide, followed by craniospinal photon radiation. They were also maintained on a hormone replacement regimen of hydrocortisone (9.1 mg/m^2/day split dose), levothyroxine (1.52 µg/kg), and desmopressin (250 µg total daily dose in split increments). Ngenla® (somatrogon-ghla, 0.66 mg/kg/week) was started 6 months later upon completion of tumor treatment.

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The patient was in complete radiographic and biochemical remission at a routine off-therapy appointment. She appeared clinically well and was meeting developmental milestones. Notable physical findings included an annualized growth rate exceeding 12 cm/year with 2.5 cm of growth since the GH therapy. However, while surveillance labs showed a serum alpha-fetoprotein of 2.8 ng/mL (reference interval, ≤10 ng/mL), a diagnostic challenge arose regarding her β-hCG monitoring. Following the initiation of GH injections approximately 1 month after completion of cancer treatment, her β-hCG levels became slightly elevated, with measurements on the Beckman Coulter platform (Unicel DxI 800) showing fluctuating positive results inconsistent with the clinical picture of complete remission. A β-hCG measurement 6 months (day 190) after the start of the GH therapy resulted in 48 mIU/mL (reference interval, 0–5 mIU/mL), whereas follow-up levels on days 196, 265, and 267 of GH therapy were <5, 7, and 36 mIU/mL, respectively (Tables 1and 2). Such variability for β-hCG levels is unusual even for nongerminomatous germ cell tumors and warranted analytical investigation.

QUESTIONS TO CONSIDER
1. What could contribute to fluctuating hCG values in blood?
2. How should unexpected variations in hCG be approached clinically?
3. What are common interferences of serum hCG measurements?

Table 1. Laboratory results at diagnosis and post-chemotherapy results.

Analytes	Reference intervals	At diagnosis	End of chemotherapy
CSF glucose, mg/dL	45–60% of serum glucose	73	47
CSF protein	0–40 mg/dL	32	19
CSF xanthochromia	Absent	Absent	Absent
CSF appearance	—	Colorless	Colorless
CSF red cell count	/mm3	4	0
CSF nucleated cell count	0–5/mm3	3	1
CSF *AFP*	<1.5 ng/mL	11	<0.5
CSF β-hCG	≤1.0 IU/L	5.1	<0.6
Serum *AFP*	≤10.0 ng/mL	47.7	2.8
Serum β-hCG	0–5 mIU/mL	14	<5

Abbreviation: *AFP*, alpha-fetoprotein.

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Table 2. Relevant serum laboratory results following GH therapy and injections.

Analytes	Reference intervals	Day 190 (+1 day)	Day 265 (+6 days)	Day 267 (+1 day)
Free thyroxine	0.7–1.5 ng/dL	1.0	0.8	0.9
TSH	0.47–4.17 mcIU/mL	0.04	—	0.02
FSH	0.4–4.2 mIU/mL	0.3	—	0.2
LH	<0.3 mIU/mL	<0.1	—	<0.1
Ultrasensitive LH	<0.02–4.8 IU/L	—	<0.02	—
Vitamin D, 25-hydroxy	30–100 ng/mL	—	27	—
Cortisol	1.9–9.7 µg/dL	—	4.5	—
Estradiol	≤35.9 pg/mL	<4.0	<4.0	<4.0
IGF-1	67–349 ng/mL	301	231	310
Sodium	135–145 mEq/L	—	139	—
Glucose	60–140 mg/dL	—	81	—
AFP	≤10.0 ng/mL	3.0	2.8	3.1
β-hCG	0–5 mIU/mL	48	7	36

Abbreviation: *AFP*, alpha-fetoprotein.

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the December 2026 issue of *Clinical Chemistry*. To view the case and comments online, go to https://academic.oup.com/clinchem/issue/72/12 and follow the link to the Clinical Case Study and Commentaries.

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