

CLINICAL VIGNETTE

A Case of HCG-Mediated Hyperthyroidism Related to Metastatic Choriocarcinoma

Samantha C. Sovich, MD¹, Dave K. Garg, MD² and Run Yu, MD, PhD²

¹Department of Medicine

²Division of Endocrinology, University of California Los Angeles, Los Angeles, CA

Introduction

Choriocarcinoma is a type of non-seminomatous germ-cell tumor that typically produces excess human chorionic gonadotropin (HCG). Due to high serum levels of HCG, patients can develop hyperthyroidism, a rare but recognized paraneoplastic phenomenon associated with choriocarcinoma.² HCG can stimulate the thyroid-stimulating hormone (TSH) receptor due to a common α -subunit, which is also similar to follicle-stimulating hormone and luteinizing hormone.¹ HCG-mediated hyperthyroidism is also observed in other germ cell tumors, hyperemesis gravidarum, and hydatidiform moles.¹

Case Description

A 21-year-old male with recently diagnosed metastatic non-seminomatous germ cell choriocarcinoma presented with persistent tachycardia and anxiety. At the time of diagnosis, he was complaining of 1 week of testicular pain, 20 pounds of unintentional weight loss, and nipple discharge. Testicular ultrasound showed a small hypoechoic area within the right testicle. Computed tomography of the abdomen and pelvis showed multiple pulmonary nodules bilaterally, multiple ill-defined hepatic lesions, and an enhancing mass in the retroperitoneum. The thyroid function tests and β -HCG levels throughout the course of his disease are depicted in **Table 1**. On initial presentation, his β -HCG was 6,435 mIU/mL (normal <1 for a male) and TSH was 1.6 mIU/mL (normal 0.3-4.7). Following four cycles of etoposide, ifosfamide, mesna, and cisplatin (VIP therapy), his β -HCG was 44 mIU/mL and TSH 0.74 mIU/mL. Three months after completion of chemotherapy, his β -HCG increased to 5,378 mIU/mL and TSH decreased to 0.14 mIU/mL. His course was complicated by seizures and metastatic brain lesions, and he underwent left parietal craniotomy and five fractions of brain radiation. One month after his procedure he developed headaches, nausea, and vomiting and was found to have metastatic brain disease on imaging. At this time, his heart rate ranged 100-120 beats per minute, and he had a blood pressure 110/70 and temperature of 98 degrees Fahrenheit. His β -HCG was 103,229 mIU/mL, TSH <0.02 mIU/mL, free thyroxine (FT4) 2.6 ng/dL (normal 0.8-1.7), and free triiodothyronine (FT3) 449 pg/dL (normal 222-383). Thyroid peroxidase antibody, thyroid stimulating immunoglobulin, and thyroid binding inhibitory immunoglobulin were all negative. The patient was initially started on

propylthiouracil in preparation for contrast imaging and then transitioned to methimazole. He was additionally started on propranolol for his persistent tachycardia. After one week of methimazole therapy, his β -HCG was >1,000,000 mIU/mL and TSH <0.02 mIU/mL. However, his FT4 was 1.5 ng/dL and FT3 was 313 pg/dL, both within the normal range. His course was complicated by hemorrhagic shock and acute liver injury in the setting of a presumed intraluminal gastric metastasis, necessitating the discontinuation of methimazole. Iopanoic acid was not available, and we were unable to use propranolol in the setting of his shock. Radioactive iodine ablation and surgery were considered, but the patient was too unstable and was continued on steroids to try to minimize T4 to T3 conversion, but ultimately his thyroid hormones uptrended. He became stable enough to tolerate five days of chemotherapy, after which his FT3 and FT4 quickly normalized. Unfortunately, he continued to suffer from vasodilatory shock and expired.

Discussion

Studies have demonstrated that HCG can bind to the TSH receptor and has thyrotropic activity.¹ In cultured rat thyroid cells, HCG stimulates iodine uptake, adenylate cyclase, and DNA synthesis.³ However, the development of hyperthyroidism requires HCG levels to be >200,000 mIU/mL for several weeks.¹ The prevalence of hyperthyroidism in choriocarcinoma is not known. However, in a study of 148 patients with disseminated non-seminomatous germ cell tumors, 3.5% of patients had hyperthyroidism.² In patients with serum HCG levels >50,000 mIU/mL, the prevalence increased to 50%.² Chemotherapy usually results in a fast decline in HCG and FT4. Interestingly, starting chemotherapy can also theoretically result in a HCG surge which can then worsen hyperthyroidism and even result in thyroid storm. It is not known whether treatment with thionamides can prevent patients from developing thyroid storm due to this surge of HCG. However, if time allows, treatment may improve patients' symptoms and result in better tolerability of any subsequent chemotherapy.²

Conclusion and Clinical Implications

Hyperthyroidism can be difficult to recognize in patients suffering from cancer as many of the typical symptoms can also

be seen with active malignancy. Patients with HCG-secreting tumors should be evaluated for hyperthyroidism and may benefit from treatment until the underlying cause can be managed.

Table 1

	Reference Range	At diagnosis	Finishing Cycle 4 of VIP chemotherapy	3 months after finishing chemotherapy	5 months after finishing chemotherapy	One week after initiating methimazole	Following dose reduced chemotherapy
B-human chorionic gonadotropin, quantitative (mIU/mL)	<1 in male	6,435	44	5,378	103,229	>1,000,000	513,363
Thyroid-stimulating hormone (mIU/mL)	0.3-4.7	1.6	0.74	0.14	<0.02	<0.02	0.10
Free Thyroxine (ng/dL)	0.8-1.7				2.6	1.5	1.0
Free Triiodothyronine (pg/dL)	222-383				449	313	199
Total Triiodothyronine (ng/dL)	85-185				150	114	

REFERENCES

1. **Hershman JM.** Physiological and pathological aspects of the effect of human chorionic gonadotropin on the thyroid. *Best Pract Res Clin Endocrinol Metab.* 2004 Jun;18(2): 249-65. doi: 10.1016/j.beem.2004.03.010. PMID: 15157839.
2. **Oosting SF, de Haas EC, Links TP, de Bruin D, Sluiter WJ, de Jong IJ, Hoekstra HJ, Sleijfer DT, Gietema JA.** Prevalence of paraneoplastic hyperthyroidism in patients with metastatic non-seminomatous germ-cell tumors. *Ann Oncol.* 2010 Jan;21(1):104-8. doi: 10.1093/annonc/mdp265. Epub 2009 Jul 15. PMID: 19605510.
3. **Hershman JM, Lee HY, Sugawara M, Mirell CJ, Pang XP, Yanagisawa M, Pekary AE.** Human chorionic gonadotropin stimulates iodide uptake, adenylate cyclase, and Deoxyribonucleic acid synthesis in cultured rat thyroid cells. *J Clin Endocrinol Metab.* 1988 Jul;67(1):74-9. doi: 10.1210/jcem-67-1-74. PMID: 3379138.