

Paraneoplastic Hyperthyroidism Secondary to a Chemotherapy-Induced Surge in β -hCG in a Patient with Non-Seminomatous Germ Cell Tumor

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Abstract

Thyrotoxicosis as the presenting syndrome of an underlying β -hCG-secreting malignancy is well described. It has been previously theorized, but not reported, that the surge of β -hCG secondary to chemotherapy induction may inadvertently trigger thyrotoxicosis. After thorough review, this is the first documented case of such event in peer-reviewed medical literature published in the English language. This is a case of a 21-year-old male with stage IIIc non-seminomatous germ cell tumor who developed paraneoplastic hyperthyroidism within 4 days of the first cycle of chemotherapy. Management considerations are suggested based on this case and review of the literature.

Keywords

paraneoplastic, thyrotoxicosis, β -hCG, germ cell tumor, malignancy

Abbreviations

β -hCG = beta human chorionic gonadotropin
TSH = thyroid stimulating hormone

Introduction

Thyrotoxicosis is a discernible manifestation of hyperthyroidism, which typically presents with heat intolerance, palpitations, anxiety, fatigue, weight loss, tremor, tachycardia, lid lag or warm moist skin. It most commonly arises in the setting of Graves' disease, toxic adenoma or multinodular goiter, exogenous thyroid hormone consumption or as an inflammatory thyroiditis.^{1,2} Rarely, thyrotoxicosis presents from trophoblastic sources, namely choriocarcinoma, molar pregnancy, hyperemesis gravidarum^{1,2} and germ-cell tumors.³⁻⁵ Testicular cancers are considered one of the most survivable malignancies with a 5-year mortality rate of only 4.5%.⁶ Despite an overall low mortality, testicular cancers are not without significant morbidity, as curative treatment involves surgery and chemotherapy.⁷ A particular subset of testicular cancers, germ cell tumors, can exhibit thyroid-stimulating behavior as a result of elevated β -hCG. In a recent prospective study of 144 patients with disseminated non-seminomatous germ cell tumors, the prevalence of hyperthyroidism was 3.5%, which increased to a prevalence of 50% in those with β -hCG levels $>50\,000$ mIU/mL (reference range: β -hCG <1.20 mIU/mL).⁸ This phenomenon, known as paraneoplastic hyperthyroidism, typically resolves during chemotherapy as the tumor burden and β -hCG secretion from the tumor diminishes precipitously with few patients requiring directed anti-thyroid treatment.^{4,8,9} However, paraneoplastic

hyperthyroidism may easily perplex clinicians as there are many overlapping features between thyrotoxicosis, malignancies, and adverse effects of chemotherapy. Therefore, providers must maintain a low-index of suspicion for this derangement to prevent a delay in diagnosis and treatment of the comorbid sequelae that accompany thyrotoxicosis.

Case Presentation

A 21-year-old previously healthy male initially presented to his primary care physician with hemoptysis, weight loss, and abdominal pain. Upon investigation he was found to have a stage IIIc non-seminomatous germ cell tumor with both pulmonary and retroperitoneal metastases (**Figure 1**) with a serum β -hCG of 136 760 mIU/mL. Subsequently, he underwent a radical left orchiectomy followed by a standard chemotherapy regimen of bleomycin, etoposide, and cisplatin. He was closely monitored during his induction phase, and on cycle 1, day 4 he developed inappropriate sinus tachycardia into the 170s, hyperhidrosis, fatigue, abdominal pain, nausea, and vomiting. He was admitted for work-up of his tachycardia, which included a 12-lead electrocardiogram reflective of sinus tachycardia, cardiac telemetry with no evidence of an arrhythmia, chest computed tomography negative for a pulmonary embolism, and normal electrolytes. His hemoglobin had mildly decreased from 8.5 to 7.7 within 24 hours, which resulted in administration of 2 units of packed red blood cells with no substantial improvement in his tachycardia. Further workup revealed a thyroid stimulating hormone (TSH) level of 0.0118 μ IU/mL (ref: 0.35-5.0 μ IU/mL), free T4 of 28.7 pmol/L (ref: 10.3-20.6 pmol/L), T3 of 1.46 ng/mL (ref: 0.8-2.0 ng/mL) and serum β -hCG $>225\,000$ mIU/mL (ref: 0-5 mIU/mL). Extensive endocrine evaluation found no primary etiology for thyrotoxicosis, including the absence of thyroperoxidase and thyroid stimulating hormone receptor antibodies and an unremarkable thyroid exam, thus proposing thyrotoxicosis arising from β -hCG stimulation from his testicular cancer, as depicted by his clinical course (**Figure 2**). Methimazole 20mg daily and 25mg atenolol twice daily were started, which resulted in resolution of his tachycardia within 48 hours. He then completed cycle 1 of chemotherapy with marked improvement of his serum tumor markers and biochemical thyroid function. Methimazole and atenolol were discontinued prior to cycle 2 of chemotherapy without clinical or serologic evidence of recurrent hyperthyroidism.



Figure 1. Computed Tomography Abdomen and Pelvis with Contrast Revealing Retroperitoneal Metastasis of a Stage IIIc Non-Seminomatous Germ Cell Tumor

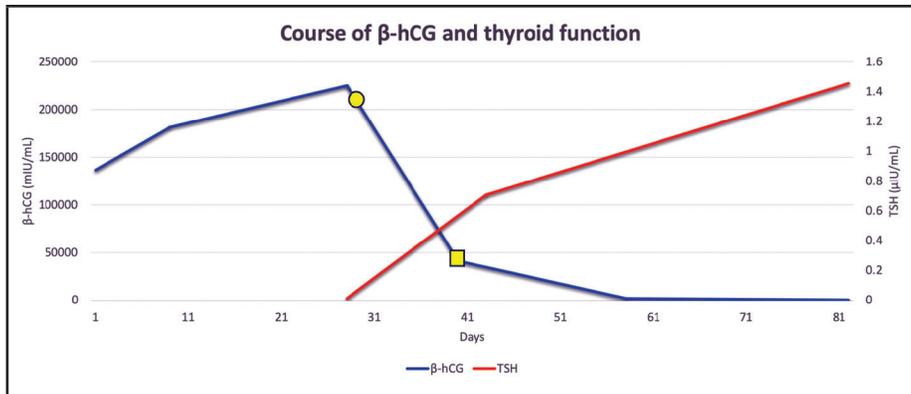


Figure 2. Course of β -hCG and Thyroid Function.

Day 1 represents diagnosis of malignancy followed by initiation of chemotherapy on day 19. Biochemical evidence of paraneoplastic hyperthyroidism was captured on day 28. Methimazole was started on day 29, as annotated by the circle, and discontinued prior to the start of cycle 2 on day 40, as annotated by the square. Clear evidence of normalized thyroid function testing with nearly undetectable β -hCG was appreciated by day 82.

Discussion

The pathophysiology of thyroid stimulation by β -hCG is attributed to cross-reactivity of the alpha-subunits of β -hCG and TSH. Additionally, there is an increased affinity for the TSH receptor if β -hCG becomes desialylated or deglycosylated, which more often is found in tumors secreting β -hCG than in cases related to an otherwise normal pregnancy.^{10,11} The prevalence of paraneoplastic hyperthyroidism is estimated at 3.5% in disseminated non-seminomatous germ cell tumors. A measure of concentration-dependency is also evident such that a β -hCG level of <50 000 mIU/mL will rarely, if ever, cause thyroid function abnormalities.⁸ Cytotoxic effects of chemotherapy induction producing a predictable surge of β -hCG, is well-described in the medical literature. β -hCG is expected to

rise at a median increase of 181% approximately 5 days after the start of chemotherapy induction, likely a result of initial tumor lysis.¹² However, iatrogenic thyrotoxicosis secondary to this predictable β -hCG surge has not been described. At the time of his tumor diagnosis, this patient had a significantly elevated β -hCG and no clinical evidence of hyperthyroidism. Baseline thyroid function testing is not routinely recommended for management of testicular cancer and was not obtained in this case. Induction of cytotoxic chemotherapy caused the predictable spike in β -hCG plausibly resulting in iatrogenic paraneoplastic hyperthyroidism.

Another consideration for his thyrotoxicosis included iodine induced thyroiditis, given his recent exposure to iodinated contrast with a computed tomography scan. However, this phenomenon

is typically present in patients from iodine-deficient regions, often in the setting of a goiter, neither of which were present in this patient. Additionally, Graves' disease was deemed less likely given the absence of thyroid stimulating hormone receptor antibodies. However, to have effectively ruled out these possibilities, a thyroid ultrasound and a radioactive iodine uptake scan could have been obtained, but these were not deemed compulsory at the time of diagnosis.

Consistent with case reports of paraneoplastic hyperthyroidism, but which were unrelated to chemotherapy induction, this patient's clinical course improved with continued treatment of his primary cancer evidenced by the inverse relationship of β -hCG and TSH.^{4,8,9} The timing of resolution after cancer treatment is unclear, therefore, initiation of treatment for thyrotoxicosis at the time of recognition is prudent. Therapy should be aimed at the comorbid sequelae of thyrotoxicosis, such as beta-blocking medications to address the tachycardia associated with thyrotoxicosis. Directed anti-thyroid treatment should also be considered, but may not always be necessary depending on the severity of presentation. Upon resolution of symptoms and normalization of serum thyroid markers, discontinuation of anti-thyroid treatment and adjunctive therapies can be considered as displayed in this patient.

Conclusion

This case demonstrates one potential adverse effect of chemotherapy resulting in paraneoplastic hyperthyroidism secondary to chemotherapy-induced surge in β -hCG in a patient with non-seminomatous germ cell tumor. As noted, there are many overlapping features between thyrotoxicosis, malignancies, and adverse effects of chemotherapy, and the complications resultant from thyrotoxicosis pose significant risks. Therefore, clinicians may consider testing serum thyroid function at baseline for patients with a β -hCG secreting tumor when serum β -hCG levels are ≥ 50 000 mIU/mL and as clinically indicated while undergoing cytotoxic chemotherapy. Early recognition and treatment of paraneoplastic hyperthyroidism may improve quality of life and reduce comorbidity, including progression to life-threatening thyroid storm.

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Conflicts of Interest

None of the authors identify a conflict of interest.

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