Diagnostic and Management Problems of Hyperthyroidism in A Patient with Testicular Seminoma

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ABSTRACT

Patients with thyroid dysfunction are well represented in the general population. Hyperthyroidism can develop as a paraneoplastic syndrome in germ cell tumors. As a form of germ cell tumors, Testicular seminoma can express human chorionic gonadotropin (hCG). Beta-hCG strongly resembles TSH. A 26-year-old male with a history of cryptorchidism came to Dr. Soetomo Hospital with complaints of palpitation, diarrhea, weight loss, fatigue, nervousness, excessive sweating, and heat intolerance. He also complained of enlarged breasts and a palpable mass in the lower abdomen for four months. The TSH and FT4 examinations showed that the patient’s symptoms were following thyrotoxicosis. Anti-TPO and thyroid USG examinations were within normal limits. The patient was treated with beta-blocker and thiamazole. Histopathology of the abdominal mass showed a testicular seminoma. After surgery and chemotherapy, the clinical symptoms of hyperthyroidism gradually improved. Administration of beta-blocker and thiamazole was stopped in 4 months after surgery. We reported a patient with symptoms of thyrotoxicosis. Thyrotoxicosis was then related to his abdominal mass, a testicular seminoma. Hyperthyroidism was treated with beta-blocker and thiamazole. The clinical symptoms of hyperthyroidism gradually improved after surgery and chemotherapy.

Keywords: Hyperthyroidism, Thyrotoxicosis, Beta-hCG, Testicular Seminoma

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Article history: •Received 27 August 2021 •Received in revised form 15 October 2021 •Accepted 1 November 2021 •Available online 31 January 2022

INTRODUCTION

Patients with thyroid dysfunction are well represented in the general population. Studies report the prevalence of abnormal thyroid function as high as 21% in women and 3% in men. Thyroid hormones play a crucial role in homeostasis due to their effects on the cardiovascular, respiratory, renal, gastrointestinal, hematologic, and central nervous systems (Palace, 2017). The term “hyperthyroidism” refers to an increase of biosynthesis and secretion of thyroid hormone by the thyroid hormone. In contrast, the term “thyrotoxicosis” refers to clinical syndromes of hypermetabolism and hyperactivity, which happens when the concentration of free thyroxine (FT4), free triiodothyronine (FT3), or both increase (Sutjahjo & Tjokroprawiro, 2015).

Hyperthyroidism can develop as a paraneoplastic syndrome in germ cell tumors. Tumor cell germinativum can express alpha-fetoprotein (AFP) and human chorionic gonadotropin (hCG). The hCG molecule has a high level of homology with thyroid-stimulating hormone (TSH) to bind to the TSH receptors and cause the clinical symptoms of hyperthyroidism (Baagar et al., 2013).

Symptomatic management of hyperthyroidism induced by germ cell tumors is not different from hyperthyroidism in general, namely administration of beta-adrenergic receptor antagonists (beta-blockers) and anti-thyroid drugs. However, definitive therapy for hyperthyroidism in malignancies that secrete hCG is the management of malignancy. The main treatment of germ cell tumors is surgery, continued by chemotherapy (Hussain & Eck, 2012).

In this report, we present a case of a young man with a history of undescended testicles who had hyperthyroidism suspected of being related to the intraabdominal tumor. The notion that hyperthyroidism was a paraneoplastic syndrome arose because there was no prior history of thyroid disorders and thyroid ultrasound examination was within normal limits. The patient underwent an open biopsy, and it was proven that the intraabdominal tumor was testicular seminoma which was one type of germ cell tumor. Clinical symptoms of thyrotoxicosis were managed with beta-blocker and anti-thyroid drugs. The clinical manifestation of hyperthyroidism improved after surgery and chemotherapy.

CASE REPORT

A 26-year-old man, Mr. MIM, having his address at Surabaya, East Java, ethnic Javanese, married, came to the Endocrinology Clinic of Dr. Soetomo Hospital on April 14, 2017, with complaints of palpitation, diarrhea, weight loss, fatigue, heat intolerance, and sleeping difficulty since the last one month. The patient also complained of nausea, abdominal discomfort, enlarged breast, and a palpable mass in the lower abdomen for four months—no complaints of fever, tightness, and coughing. The patient had been married for almost two years and has no children. The patient only has one testicle from birth.

Physical examination of the patient showed the awareness was compos mentis, GCS of 456, and visual analog scale (VAS) of 0. Vital signs: blood pressure of...
130/80 mmHg, pulse rate of 105 times/minute, respiratory rate of 20 times/minute, temperature 37.8°C. On examination of the head and neck, no exophthalmos was found, and no thyroid gland enlargement was obtained. On examination of the abdomen, mild ascites and mass were found in the suprapubic region with a diameter of approximately 10 cm, painless in palpation. Examination of the thorax and the extremities were within normal limits.

On May 15th, 2017, a laparotomy and open biopsy of the abdominal tumor were performed. Towards the operation, thiamazole and propranolol therapy were continued. From histopathological examination of abdominal tumor tissue, malignant germ cell tumors with seminoma dominance and choriocarcinoma were found.

On May 29th, 2017, patient was hospitalized in Internal Medicine ward and planned for chemotherapy. Complaints of abdominal discomfort, palpitations, and fatigue had improved. Vital signs: blood pressure of 110/80 mmHg, pulse rate of 90 times/minute, respiratory rate of 20 times/minute, temperature of 37.0°C. Laboratory examination demonstrated hemoglobin of 9.7 g/dL, MCV of 86 fl, MCH of 31 pg, leucocyte count of 6.890/μL with neutrophils of 67.0%, platelet count of 340,000/μL, blood glucose of 91 mg/dL, ALT of 23 U/L, AST of 40 U/L, BUN of 10 mg/dL, serum creatinine of 0.74 mg/dL, total quantitative beta-HCG of 72,000 IU/mL (normal: <3), total T3 of 1.13 pg/mL (normal: 0.60-1.81), total T4 of 15.7 ng/mL (normal: 4.50-10.90), TSH of 0.1 mIU/mL (normal: 0.55-4.78), FT3 of 3.9 pg/mL (normal: 2.3-4.2), FT4 of 2.18 ng/dL (normal: 0.89-1.76), and anti-TPO of 10.8 IU/mL (normal: <35).

The patient was diagnosed with hyperthyroidism, testicular seminoma, and normochromic normocytic anemia. The patient received a blood transfusion to fulfill the chemotherapy requirement, i.e., hemoglobin >10 g/dL. The patient received chemotherapy with the BEP regimen, namely Bleomycin 30 mg (days 2, 9, and 16), Etoposide 100 mg (days 1-5), and Cisplatin 20 mg (days 1-5). Treatment for hyperthyroidism was continued with dose adjustment: thiamazole 10 mg once daily and propranolol 10 mg twice daily.

Chemotherapy with the BEP regimen was given in 3 cycles at 21 days intervals. The patient came to Endocrinology Clinic once a month. One month after surgery (June 2017), abdominal complaints, palpitation, and fatigue were improved. Laboratory examination showed total quantitative beta-HCG of 12,000 IU/mL (normal: <3), TSH of 0.1 mIU/mL (normal: 0.55-4.78), FT3 of 3.5 pg/mL (normal: 2.3-4.2), FT4 of 2.02 ng/dL (normal: 0.89-1.76). Treatment for hyperthyroidism was adjusted in dose: thiamazole 5 mg once daily and propranolol 10 mg once daily.

In the fourth month post-surgery (September 2017), the patient had no complaints. Laboratory examination showed total quantitative beta-HCG of 320 IU/mL (normal: <3), TSH of 0.60 mIU/mL (normal: 0.55-4.78), FT3 of 3.9 pg/mL (normal: 2.3-4.2), FT4 of 1.72 ng/dL (normal: 0.89-1.76). Treatment for hyperthyroidism was stopped as the patient had reached the euthyroid condition.

**DISCUSSION**

The paraneoplastic syndrome was first described in the 1940s when it was recognized that certain neoplasms might cause various symptoms that are not solely attributable to direct tumor invasion, compression, and the development of metastases. Such neoplasms present or acquire in time the ability to secrete various biologically-active substances that can lead to the development of distinctive clinical syndromes. Paraneoplastic syndromes can be the product of tumor-secreted peptides, amines or cytokines, or immune cross-reactivity between neoplastic and normal tissues. They can originate from either endocrine or non-endocrine neoplasms (Pelosof & Gerber, 2010). Endocrinology's most
common paraneoplastic syndromes are hypercalcemia, SIADH, Cushing syndrome, hypoglycemia, acromegaly, ectopic beta-hCG production, ectopic gonadotropin production, and hypoadosteronism (Dimitriadis et al., 2017).

Testicular neoplasms comprise the most common solid malignancy affecting men between 15 and 35, but they only represent almost 1% of all solid tumors in males. Approximately two to three new cases per 100,000 males are reported in the United States each year, and 95 percent of all primary testicular tumors are germ cell tumors (Baagar et al., 2013). Germ cell tumors are divided into seminomatous or non-seminomatous types (Hussain & Eck, 2012). About 10% of all testicular cancers are associated with cryptorchidism, with the highest risk with abdominal testis. Other than infertility, associated inguinal hernia and torsion, malignant change in the undescended testicle is a common complication (Bose et al., 2017). The cryptorchidism results from abnormalities in the formation and testicular descent during the embryonic period. The most common malignant transformation of an undescended testicle is testicular seminoma (Carliotto et al., 2015).

Testicular tumors usually present as a nodule or painless swelling of one testicle, which may be noted incidentally by the patient. Approximately 30 to 40 percent of patients complain of a dull ache or heavy sensation in the lower abdomen, perianal area, or scrotum, while acute pain is the presenting symptom in 10 percent. The presenting manifestations of testicular cancer are attributable to metastatic disease in approximately 10 percent of patients. Symptoms vary with the site of metastasis, such as anorexia, nausea, vomiting, or abdominal pain due to retroperitoneal metastasis. The paraneoplastic syndromes of testicular tumors are hyperthyroidism and gynecomastia (Taslimi, 2011).

In this patient, there was a history of cryptorchidism. The patient had only one testicle from birth. The patient complained of abdominal discomfort, palpable mass in the lower abdomen, and enlarged breasts for the last four months. From histopathological examination of abdominal tumor tissue, malignant germ cell tumors with seminoma dominance and chorioniccarcinoma were found. Germ cell tumors express either alpha-fetoprotein (AFP) or human chorionic gonadotropin (hCG). Intact hCG consists of two subunits, i.e., alpha and beta subunits. Beta-hCG levels are an important tool in diagnosing and monitoring the treatment of germ cell tumors (Hussain & Eck, 2012).

Hyperthyroidism is a manifestation of the paraneoplastic syndrome in germ cell tumors. The clinical symptoms may vary from an absence of symptoms, thyrotoxicosis, to thyroid storm. Hyperthyroidism presents clinically as a physiological state dominated by an increased metabolic rate: myocardial contractility, heart rate, stroke volume, and ventricular size increase. Peripheral vascular resistance decreases inskinandmuscle. Typical clinical findings include fatigue, weight loss, nervousness, excessive sweating, heat intolerance, hyperactivity, tremor, weakness, hyperdynamic precordium, diarrhea, increased appetite, muscle weakness, and tachycardia, minimal or without enlargement of the thyroid gland (Kurdi, 2014). Hyperthyroidism which manifests as thyrotoxicosis, can usually be seen in patients with very high hCG levels. It presents in 3.5% of the patients with germ cell tumors and 50% of the patients with hCG above 50,000 IU/L (Baagar et al., 2013).

In this patient, there were symptoms of palpitation, abdominal discomfort, weight loss, fatigue, sleeping difficulty, and heat resistance, which were in accordance with thyrotoxicosis. Increased hCG expression occurs in germ cell tumors and pregnancy and hydatiform moles. hCG is a glycoprotein with structural similarities with TSH (Meister et al., 2005). hCG is a heterodimer composed of an alpha-subunit and beta-subunit. hCG alpha-subunit is common to all the glycoprotein hormones (follicle-stimulating hormone/FSH, luteinizing hormone/LH, TSH). hCG and TSH beta-subunits are highly homologous, and both contain 12 half-cysteine residues and one N-linked oligosaccharide. Three disulfide bonds from a cystein knot structure are identical in both hormones (Sotello et al., 2016).

Several data indicate that hCG is a weak human thyrotropin. Due to its homology, it also activates the TSH receptor. But the relative potency of hCG for the TSH receptor is 4000 times less than TSH. High circulating hCG levels with their TSH-like activity may result in a slightly low TSH and an increase in FT4 concentration. It is estimated that an increment of hCG of 10,000 IU/mL results in a decrease in TSH of 0.1 mU/L and an increase of FT4 of 0.6 pmol/L. The level of hCG largely influences the development of hyperthyroidism due to hCG. Clinically measurable changes in thyroid hormone concentration are only likely if hCG levels are around 50,000-70,000 IU/mL or more (Kurdi, 2014). More than 40% of patients with beta-hCG over 50,000 IU/mL have biochemical hyperthyroidism (Hussain & Eck, 2012). Serum levels of hCG of >100,000 IU/mL are usually needed to produce clinical evidence of thyrotoxicosis (Kurdi, 2014).

Not all patients with significantly elevated hCG levels develop hyperthyroidism and thyrotoxicosis. This is thought to be related to hCG variants with different isoforms having different thyroid-stimulating activity and the presence of polymorphisms of the TSH receptor genes (Hussain & Eck, 2012). Secondary modifications of hCG such as sialylation or glycosylation can affect hCG bioactivity and the sensitivity of the TSH receptor to hCG (Sotello et al., 2016).

Elevated thyroid hormone levels may affect the pituitary-gonadal axis, the metabolism of sex steroid hormones, and the estrogen/androgen action at the breast tissue level. A British case study suggests an association between hyperthyroidism, hypogonadism, and gynecomastia, hypothesizing that the male breast may be more susceptible to a subtle change in estrogen/androgen balance in the presence of both hypogonadism and hyperthyroidism. Hyperthyroid men are reported to have increased FSH and LH and decreased free testosterone. Gynecomastia is observed in 20-40% of men with hyperthyroidism, and thyroid hormones are elevated in ~2% of newly
referred patients with gynecomastia (Mieritz et al., 2014).

In this patient, there was an increase in beta-hCG levels, which reached >150,000 IU/mL at the early time of diagnosis. This beta-hCG hormone was produced by a germ cell tumor (testicular seminoma). High levels of beta-hCG hormone affected the balance of estrogen/androgen, so the patient developed gynecomastia. High levels of beta-hCG are also bound to the TSH receptor causing symptoms of hyperthyroidism.

Serum TSH measurement has the highest sensitivity and specificity of any single blood test used in the elevation of suspected thyrotoxicosis and should be used as an initial screening test. Diagnostic accuracy improves when serum TSH and FT4 are assessed at the initial evaluation. The relationship between FT4 and TSH when the pituitary-thyroid axis is intact is an inverse log-linear relationship; therefore, small changes in FT4 result in significant changes in serum TSH concentrations (Ross et al., 2016). Thyrotoxicosis is diagnosed when FT4 is higher than usual, but TSH is suppressed. When FT4 is normal, but TSH is low, it is valuable to measure FT3; when the latter is abnormally high, the diagnosis is T3-toxicosis. When both FT4 and FT3 are normal, but TSH is low, “subclinical thyrotoxicosis” can be applied (Mitra et al., 2008).

To exclude the suspicion of Graves’ disease as a cause, and anti-TPO examination also needs to be performed. Anti-TPO (TPO-Ab) is a common autoantibody against Thyroid Peroxidase (TPO). Historically, anti-TPO were detected as thyroid microsomal antibodies using agglutination or immunofluorescence methods. In 1985, TPO was recognized as the target antigen of thyroid autoantibodies. Eighty percent of Graves’ disease patients have high anti-TPO antibodies, while positive anti-TPO Ab is detected in over 90% of patients with autoimmune thyroid disease. In the community, the prevalence of TPO-Ab is 11-12% euthyroid subjects (Tan & Aw, 2018).

Thyroid ultrasound was performed to see if there was a lump or nodule in the thyroid gland, which could cause hyperthyroidism. However, the thyroid ultrasound showed the thyroid gland was normal. Patients also underwent an additional examination of anti-TPO to exclude the autoimmune cause of thyrotoxicosis, but anti-TPO was also found to be normal, at 10.8 IU/mL (normal: <35). Thus, according to the very high result of beta-hCG levels, the normal result of thyroid ultrasound, and the normal results of anti-TPO, thyrotoxicosis in this patient was related to beta-hCG-induced hyperthyroidism due to germ cell tumor (testicular seminoma).

Standardized recommendations for treating hCG-induced hyperthyroidism in patients with testicular cancer do not exist. Patients with symptomatic hyperthyroidism are treated with beta-adrenergic receptor antagonist therapy and/or anti-thyroid drugs. Anti-thyroid medications are an efficacious adjuvant treatment in hCG-induced hyperthyroidism since hormone synthesis occurs within the thyroid gland. However, hyperthyroidism in hCG-secreting malignant disease represents a paraneoplastic syndrome. Therefore, the definitive treatment is the treatment of cancer (Hussain & Eck, 2012).

Surgical removal of the tumor in the case of germ cell tumors rapidly cures hyperthyroidism and should be performed as soon as possible. Therapy of hyperthyroidism is not indicated in most cases since the evacuation of the tumor or chemotherapy, removing high levels of hCG, cures the hyperthyroidism. Therapy of hyperthyroidism is only indicated in thyrotoxicosis or over hyperthyroidism. In those cases of severe symptoms, Lugol’s solution, intravenous iodine, and beta-blocking agents are indicated. Therapy with potassium iodide given orally or sodium iodide given intravenously will rapidly reduce serum-free T4 and T3 levels. Propranolol and other beta-adrenergic antagonist drugs are helpful to control tachycardia and other symptoms of sympathetic activation. Supportive measures such as fluid and electrolyte replacement should be done as needed (Taslimi, 2011).

Preoperative evaluation of these patients should be based on history, physical examination, and laboratory testing. The patient must be admitted to an intensive care unit pre-operatively. Blood count, electrolytes, blood gases, thyroid, hepatic, renal functions, β-hCG, and chest radiogram should be carefully evaluated. Treatment has to be individualized. The patient can be prepared for the surgery with oral propylthiouracil (50-100 mg qid), propranolol (20 mg tid), intravenous glucocorticoids, and sodium iodide. Some cases may require only beta-blockers, whereas others may require additional anti-thyroid drugs. Some may not require any treatment if the hyperthyroidism is only biochemical and asymptomatic (Kurdi, 2014).

In patients in whom the diagnosis of thyrotoxicosis is strongly suspected or confirmed, treatment with propranolol, atenolol, metoprolol, or other beta-blockers leads to a decrease in heart rate, systolic blood pressure, muscle weakness, and tremor, as well as improvement in the degree of irritability, emotional lability, and exercise intolerance. Since there is insufficient beta-1 selectivity of the available beta-blockers at the recommended doses, these drugs are generally contraindicated in patients with bronchospastic asthma. However, in patients with quiescent bronchospastic asthma in whom heart rate control is essential, a nonselective beta-blocker such as nadolol can be used cautiously, with careful monitoring of pulmonary status (Ross et al., 2016).
In this patient, the thyrotoxicosis condition was managed symptomatically with the administration of beta-blocker, i.e., propranolol and anti-thyroid drug, i.e., thiamazole. The patient received thiamazole 10 mg twice daily and propranolol 10 mg three times daily orally. The treatment for hyperthyroidism aimed to relieve the complaints and minimize the risk of the emergence of a perioperative thyroid crisis.

In patients with germ cell tumors, therapy mainly consists of tumor removal and chemotherapy (Meister et al., 2005). In stage III seminoma, chemotherapy with the BEP regimen (bleomycin, etoposide, and cisplatin) is standard treatment; three cycles for good prognosis patients according to the International Germ Cell Cancer Collaborative Group/IGCCCG (alternatively four cycles of EP) and four cycles for intermediate prognosis patients according to IGCCCG (or four cycles of etoposide, ifosfamide, and cisplatin (VIP), if there are arguments against Bleomycin). Chemotherapy is repeated every 21 days. One cycle of chemotherapy consisted of cisplatin 20 mg/m2 intravenously (days 1-5), etoposide 100 mg/m2 IV (days 1-5), and bleomycin 30 mg (days 2, 9, and 16) intravenously. Bleomycin can be replaced by ifosfamide so that the VIP regimen (VP-16/etoposide, ifosfamide, platinum) is used (Oldenburg et al., 2013; Handayani, 2015).

Chemotherapy may produce an initial HCG surge, and patients should be monitored for signs of thyrotoxicosis or thyroid storm, but it is usually followed by normalization of thyroid function if the underlying disease is responsive to treatment (Sotello et al., 2016). This patient was treated with BEP regimen chemotherapy, namely Bleomycin 30 mg (days 2, 9, and 16), Etoposide 100 mg (days 1-5), and Cisplatin 20 mg (days 1-5). During chemotherapy, therapy for hyperthyroidism continued with dose adjustments as the clinical symptoms of hyperthyroidism have improved. Patients received thiamazole 10 mg once daily and propranolol 10 mg twice daily. BEP chemotherapy was administered in 3 cycles at 21 days intervals. In germ cell tumors, almost all of which respond well to effective tumor chemotherapy, beta-hCG-induced hyperthyroidism in germ cell tumors. Tumor relapse can also be associated with recurrence of thyrotoxicosis (Gama, 2001). Seminoma is one of the curable cancers, with cure rates nearing 100% even in stage II disease with surgery and radiotherapy (Bose et al., 2017). Serum TSH may remain suppressed for several months after therapy begins. Therefore TSH is not a suitable parameter for early monitoring of treatment. When thyroid levels have stabilized, a reduction in the dose of 30-50% is recommended, while examinations are repeated within 4-6 weeks (Ross et al., 2016). Most patients with symptomatic paraneoplastic hyperthyroidism will respond quickly after therapy, although some patients require postoperative intensive care due to the emergence of a thyroid crisis (Walkington et al., 2011).

After undergoing surgery and chemotherapy for three cycles, the clinical symptoms of hyperthyroidism inpatients significantly improved. Laboratory parameters, including beta-hCG, TSH, FT4, and FT3, gradually improved and approached normal. Finally, in the fourth-month post-surgery, therapy of hyperthyroidism which consisted of propranolol and thiamazole, was stopped as the patient had reached the euthyroid condition.

SUMMARY

A 26-year-old male patient with a history of cryptoridismus had been reported with complaints of palpitation, diarrhea, weight loss, fatigue, and sleeping difficulty. Patients also complained of a palpable mass in the lower abdomen and slightly enlarged breasts. From the investigation of TSH and FT4, the patient's clinical symptoms were found in accordance with thyrotoxicosis. Anti-TPO examination and thyroid ultrasound were within normal limits. Patients were treated with beta-blocker and anti-thyroid drugs. Histopathology from a sample of intra-abdominal mass obtained from the open biopsy showed a testicular seminoma. Post-surgery and chemotherapy with the BEP regimen, the clinical symptoms of hyperthyroidism significantly improved. Beta-blocker and anti-thyroid drug therapy were stopped four months after surgery as the patient had reached the euthyroid condition.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

REFERENCES


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