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Coriocarcinoma con hipertiroidismo mediado por hCG

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CASE REPORT

We present a case of a man in the early 30’s, with a history of cryptorchidism and orchidopexy in infancy and a euthyroid thyroid nodule, presented with nausea, constipation, and abdominal pain. An abdominal radiography showed no abnormalities. One month later,

after multiple visits to the emergency room, an abdominal computed tomography was performed, that showed a retroperitoneal mass of 90 × 77 × 72 mm, and multiple bilateral pulmonary nodules. Laboratory results showed pancytopenia with neutropenia and hCG levels of 144,690 mUI/mL (reference value: < 2.5). A testicular ultrasound showed no abnormalities. The patient was admitted with a presumptive diagnosis of extragonadal choriocarcinoma with pulmonary metastases and treatment was started with corticotherapy and chemotherapy, with a regimen of bleomycin, etoposide and platinum (BEP).

Approximately a week later, the patient presented with respiratory insufficiency and haemoptysis, secondary to haemorrhagic pulmonary metastasis. He was admitted to the intensive care unit for ventilatory support, and corticotherapy dose was increased. Because of the pulmonary toxicity related to bleomycin, he was started on a different chemotherapy regimen with etoposide, ifosfamide and cisplatin (VIP). During the course of treatment, the patient presented with periods of sinusal tachycardia and subfebrile temperature. On the ninth day of chemotherapy, bloodwork showed maximum hCG levels of 590,399 mUI/mL. Blood count still showed pancytopenia with neutropenia and thyroid function showed: free thyroxine (fT4) 7.77 (0.80-1.67) ng/dL, free triiodothyronine (fT3) 18.5 (2.00-4.40) pg/mL and TSH < 0.005 (0.270-4.200) uUI/mL. The patient was already on methylprednisolone 80 mg/day and was started on methimazole 25 mg/day. Later results showed negative anti-TSH receptor, anti-thyroglobulin and anti-thyroid peroxidase antibodies.

The patient continued treatment, with a favourable response: on the twenty-first day of chemotherapy, hCG levels dropped to 25,656 mUI/mL, pancytopenia and neutropenia improved, and thyroid function showed fT4 levels of 3.74 ng/dL and fT3 levels of 4.70 pg/mL. The patient was later discharged with prednisolone 40 mg/day, with a tapering protocol, methimazole 40 mg/day and propranolol 20 mg/day, with an additional 20mg/day as needed. Approximately 3

months later, the patient is still on chemotherapy and methimazole 35 mg/day, thyroid function has improved, as shown in table I, and hCG levels have significantly decreased (58.9 mUI/mL).

DISCUSSION

Hyperthyroidism secondary to excessive production of human chorionic gonadotropin (hCG) is a rare condition. We describe a case of a male patient diagnosed with choriocarcinoma, who developed hyperthyroidism in this context.

Choriocarcinoma, a non-seminomatous germ cell neoplasm, can be gestational or non-gestational. Non-gestational (or extragonadal) choriocarcinomas are a rare malignancy in men, representing only 5 % of germ cell tumours, and are usually highly invasive with a poor prognosis (1,2). These tumours typically present with very high serum levels of hCG. The structural similarity of this glycoprotein to the thyroid stimulating hormone (TSH) may lead to its biding to TSH receptors, resulting in hyperthyroidism.

Similar to luteinizing hormone (LH), follicle stimulating hormone (FSH) and TSH, hCG is a glycoprotein made up of two subunits: alpha and beta. All of them share the same amino acid sequence in their alpha subunit, and it’s their beta subunit that carries specific information which determines their binding to specific hormonal receptors. However, hCG and TSH’s beta chains also share some similarities: they both contain 12 half-cysteine residues and one N-linked oligosaccharide, and there is a cysteine structure identical in both hormones (3). These similarities may justify the ability of hCG to cross react with the TSH receptor found in several studies (3,4), which in turn leads to the paraneoplastic hyperthyroidism reported in this case.

hCG is normally produced in placental trophoblastic cells. The action of hCG is similar to that of LH because it also stimulates the *corpus luteum* to produce progesterone that helps maintain pregnancy by preventing menstruation (5). In non-pregnant woman or in man, it can

be elevated in conditions such as germ cell tumours and gestational trophoblastic disease (6). In 40 % to 60 % of men with testicular carcinoma, this hormone may be elevated, and the detection of serum hCG in extremely high amounts is often associated with invasive disease (5,7). In the case of choriocarcinoma, cell growth, blockage of apoptosis and production of invasive enzymes such as collagenases and metalloproteinases are mediated by hCG (1). In our laboratory, the measurement of hCG is performed by an electrochemiluminescence immunoassay which uses a pair of monoclonal antibodies to quantify this molecule.

Serum hCG, given its structural similarity to TSH, has been proven to have weak thyroid stimulating activity. During pregnancy, TSH levels drop when hCG levels are at their peak, and in women with hydatidiform moles or trophoblastic cancer, in which HCG levels are elevated, hyperthyroidism is a well-known phenomenon (7). Although there is no well-defined cut-off of the value at which hCG influences thyroid function, reports suggest that when hCG levels are above 50,000 mIU/mL, thyroid function should be monitored, regardless of the cause of hCG excess (7).

When the patient started chemotherapy, hCG rose to a maximum value of 590,399 mIU/mL (table I, 10th day). This phenomenon is described in other reports (7) as a result of tumour cell destruction and release of intercellular molecules into the blood stream. Consequently, the significant increase in thyroid hormones, with simultaneous symptoms of hyperthyroidism, motivated the implementation of methimazole. hCG values later dropped (from 590,399 to 58.9 mIU/mL), with concomitant decrease in fT3 and fT4 values, with clinical improvement.

Hyperthyroidism symptoms can be difficult to recognize in patients with this type of malignancy and paraneoplastic syndromes - symptoms like fatigue and weight loss overlap with those of metastatic disease. Given this, the laboratory must play an active role in the interpretation of the results, and add other parameters if

deemed appropriate, in order to bring the best possible follow-up to the patient. The introduction of antithyroid drugs in this case allowed the patient to better tolerate the chemotherapy treatments. Simultaneous measurement of hCG and fT3 and fT4 values seems to be useful in monitoring the effectiveness of the treatment (5).

KEY POINTS TO REMEMBER

- Choriocarcinoma is a rare neoplasm whose diagnosis is characterized by elevated HCG.
- There are reports of hyperthyroidism due to a considerable increase in HCG.
- It is important to be aware of paraneoplastic hyperthyroidism in choriocarcinoma.
- Antithyroid drug treatment appears to be of benefit to patients during chemotherapy for choriocarcinoma.

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Table I. Progression of hormonal values since the first day of diagnosis

	Day 1	**Day 10**	**Day 19**	**Day 21**	**Day 41**	**Day 83**
hCG R.V.: < 2,5 mUI/mL	144,960	590,399	42,995	25,656	3,276	58.9
fT3 R.V.: 2,00-4,40 pg/mL	-	18.5	2.66	2.58	2.07	3.15
fT4 R.V.: 0,80-1,67 ng/dL	-	> 7.77	3.00	2.47	1.15	1.20
TSH R.V.: 0,270-4,200 uUI/mL	-	< 0.005	< 0.005	< 0.005	0.029	0.216

R.V.: reference value.