Hyperthyroidism Due to Secretion of Human Chorionic Gonadotropin in a Patient With Metastatic Choriocarcinoma

apresentação de casos

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ABSTRACT

A 26-year-old pregnant woman presenting with repeated episodes of vaginal bleeding, weight loss, and shortness of breath was diagnosed with choriocarcinoma with metastases to both lungs. Chorionic gonadotropin levels (hCG) were >2.5 x 10^6mU/mL. Consistent with hCG-induced subclinical hyperthyroidism, she had a suppressed TSH of 0.037mU/L (0.49 - 4.67), a T4 of 18.1µg/dL (4.9 - 10.7), and T3 of 136ng/dL (45 - 137). Chemotherapy with a combined regimen with etoposide, methotrexate, and dactinomycine was started. The initial course was complicated by urosepsis with respiratory distress requiring endotracheal intubation for 3 days. She then improved rapidly, and her thyroid function tests were within normal limits by day 12. Six months later, after ten cycles of chemotherapy, the patient was in remission without signs of residual tumor or hCG-induced paraneoplastic activity. **(Arq Bras Endocrinol Metab 2005;49/2:319-322)**

Keywords: Subclinical hyperthyroidism; Choriocarcinoma; Lung metastases

RESUMO

Hipertireoidismo Secundário à Secreção de Gonadotrofina Coriônica Humana em Paciente Com Coriocarcinoma Metastático.
Relatamos o caso de uma gestante de 26 anos apresentando episódios de sangramento vaginal, perda ponderal e dispnéia, que recebeu o diagnóstico de coriocarcinoma com metástases pulmonares. O nível de gonadotrofina coriônica (hCG) era >2,5 x 10^6mU/mL. O TSH era de 0,037mU/L (0,49 - 4,67), o T4 de 18,1ug/dL (4,9 - 10,7), e o T3 de 136ng/dL (45 - 137), confirmando o quadro de hipertireoidismo subclínico induzido pela hCG. A paciente foi submetida a um regime combinado de quimioterapia com etoposídeo, metotrexate e dactiomicina. A evolução inicial foi complicada por um quadro de urosepsis com insuficiência respiratória, necessitando entubação endotraqueal por 3 dias. Após, houve melhora progressiva com normalização dos testes de função tireoideana no 12º dia de internamento. Após 6 meses e 10 ciclos de quimioterapia, a paciente estava em remissão e sem sinais de tumor residual ou de atividade paraneoplásica dependente de hCG. **(Arq Bras Endocrinol Metab 2005;49/2:319-322)**

Descritores: Hipertireoidismo subclínico; Coriocarcinoma, Metástases pulmonares

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ASIDE FROM DIABETES MELLITUS, hyperthyroidism is the most common endocrinopathy in pregnancy. Its prevalence is about 0.05 to 0.2% (1). Its clinical assessment may be difficult because many of the symptoms of hyperthyroidism are also associated with normal pregnancy. Hyperthyroidism during pregnancy is most commonly caused by Graves' disease.

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During early pregnancy, secretion of the placental hormone hCG may result in subclinical or overt hyperthyroidism (2-5). Because of the decrease of both the levels and bioactivity of hCG as pregnancy proceeds, this form of hyperthyroidism is typically transient and limited to the first 3 to 4 months of gestation. Elevations of hCG are particularly pronounced in twin pregnancies (6). Only rarely, hyperthyroidism is caused by trophoblastic tumors, hydatiform moles, and choriocarcinomas that secrete high amounts of hCG (7). In men, choriocarcinomas can arise in the testis (8-10).

HCG is a heterodimer composed of an α-subunit common to the glycoprotein hormones (LH / CG, FSH, TSH), and a β-subunit with significant homology to the β-TSH (7). At high levels, hCG interacts not only with its cognate receptor, but also with the TSH receptor, a G-protein coupled transmembrane receptor with high homology to the LH / CG receptor (7,11).

CASE REPORT

A 26-year-old woman was admitted to the hospital because of vaginal bleeding and dyspnea. She had been well until one year earlier, when she experienced significant vaginal bleeding requiring red cell transfusions. Uterine curettage was performed at this time. She then received hormonal therapy (etinilestradiol plus levonorgestrel) for 8 months. Twenty days prior to admission she developed a second episode of severe vaginal bleeding for which she again underwent uterine curretage and transfusion. Several vaginal lesions were observed and biopsied, the histology evidenced gestacional trophoblastic disease, type choriocarcinoma. Eleven days prior to the most recent hospital admission, the patient developed thoracic pain and dyspnea. At that time, she reported a one month history of anorexia accompanied by a weight loss of 13kg. A clinical diagnosis of pneumonia was made and she was treated with penicillin. She was then referred to our service.

The patient's past medical history was significant for 3 normal pregnancies, the last of which ended 2 years prior to this hospitalization. The review of systems was notable for regular menstrual cycles. She has smoked one pack of cigarettes since the age of 16.

On physical examination, the patient appeared poorly nourished, with a body mass index of 18.1kg / m^2. Temperature was 36.5ºC; pulse 90 bpm, blood pressure 100 / 70mmHg, and respiratory rate 30 ipm. Rales were audible over both lungs. The thyroid gland was normal in size and texture. On gynecological examination, there were 2 vaginal bleeding lesions that were sutured. Laboratory tests are summarized in table 1. A hCG level, performed due to a suspicion of choriocarcinoma, was found to be 2,564,768mU / mL. A chest X-ray showed multiple consolidations in both lungs suggestive of metastases (figure 1). This, together with the very high hCG level, was consistent with the diagnosis of metastatic choriocarcinoma. CT of the head and abdomen were normal.

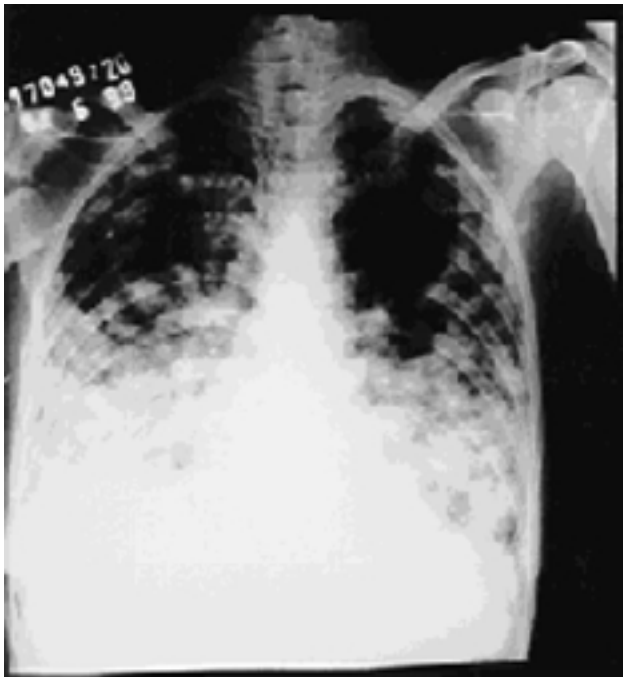

Figure 1. Chest radiography with multiple well circumscribed nodular alterations.

On the second day, chemotherapy with etoposide 155mg, and methotrexate 155mg was initiated. On day 3, she was treated with dactinomycine 0.5mg, methotrexate 310mg followed by 15mg of folic acid.

The patient then started with subfebrile temperature of 37.4ºC and developed respiratory distress, which eventually required transfer to the Intensive Care Unit. Her blood gas values were pH: 7.4, PCO^2: 21.8mmHg / KPA, PO^2: 80mmHg / KPA, HCO^3: 14.9mmol / L, BEB: -6.3mmol / L, BB: 41.7mmol / L, $\%SO^2$: 96.5%. *E. coli* grew in one urine and 3 blood cultures suggesting urosepsis. She was therefore treated with ceftriaxone and amikacin. On day 4, the patient developed fever of 38.6ºC, worsening respiratory distress, tachycardia of 140bpm and mental confusion. An endotracheal tube was inserted, and assisted ventilation was begun. Despite stabilization of her respiratory status, she continued to remain tachycardic with heart rates ranging between 160 and 190bpm. An eletrocardiogram study revealed sinus tachycardia.

Thyroid function tests performed on day 4 documented a suppressed TSH and an elevated total

Table 1. Synopsis of laboratory tests.

Day	1st	4th	12th	180th	Normal
Hemoglobin (mg/dl)	5.9	7.7	10	–	12.5 – 15.7
Hematocrit (%)	17.7	22.8	29.9	–	36.7 – 46.3
White Blood Cells	9,900	4,100	700	–	4,300 – 10,000
Linfocytes (%)	14	15	–	–	
Band Forms (%)	4	16	–	–	
TSH (uIU/mL)	–	0.037	0.204	2.57	0.49 – 4.67
hCG (mIU/mL)	2,564,768	–	4,075	75	< 5
T3 (ng/dL)	–	136.3	50.4	139.0	45 – 137
Total T4 (ug/dL)	–	18.1	–	–	4.9 – 10.7
Free T4 (ng/dL)	–	–	0.83	1.24	0.71 – 1.85
Anti–Tg–Ab (U/mL)	–	negative	–	–	< 40
Anti–TPO–Ab (U/mL)	–	negative	–	–	< 35
Trab (U/L)*	–	negative	–	–	< 10

* Trab: antibodies against TSH receptor

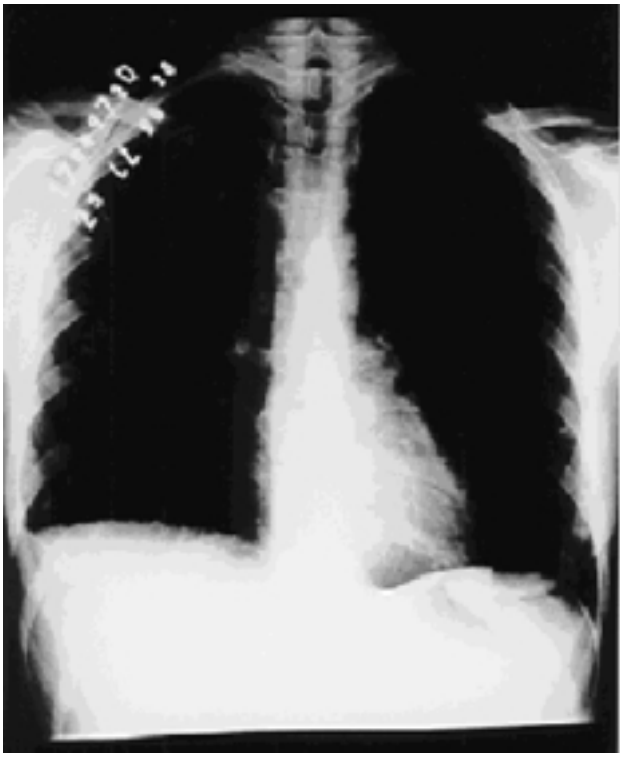

Figure 2. Chest radiography after treatment.

T4 (table 1). Antithyroid antibodies were negative. Propranolol was administered through the nasogastric tube and the heart rate declined to 100bpm.

On day 7, ceftriaxone was substituted for cefepime because of persistent fever. Radiography of the chest documented improvement of signs of ards and she could be weaned from the ventilator.

Twelve days after admission, she became afebrile, was hemodynamically stable, her respiratory rate was 20 ipm with an oxygen mask with 10L / min and her O_2 arterial blood saturation was 99%. Thyroid function tests showed normal values for TSH, FT4 and T3 (table 1).

Six months later, after completing 10 cycles of chemotherapy with etoposide, methotrexate dactinomycine and folic acid, the patient was in good general condition. Her chest X-ray was free of metastatic lesions (figure 2). Her thyroid function tests were normal and a radioiodine uptake study, with 100uCi of 131-I, was 6.3% at 2hs, and 20.1% at 24hs (Normal: 9±3% at 2hs, 25±5 % at 24hs).

DISCUSSION

Human chorionic gonadotropin may result in hyperthyroidism through crossreaction with the TSH receptor (7,12). This form of hyperthyroidism may be associated with trophoblast neoplasms such as hydatiform moles, choriocarcinomas, embryonal cell carcinomas, teratocarcinomas and testicular carcinomas (7,9,10,13-16). There is a partial correlation between hCG concentration and the severity of the hyperthyroid metabolic state (25,000U / L of hCG are roughly equivalent to 1mU / L of TSH activity) (7,15). However, secondary modifications of hCG such as sialiation do affect its bioactivity and hCG variants with thyrotropic activity have been identified. Most commonly, the hCG-induced alteration of thyroid function results in suppression of TSH and elevation of free T4. T3 levels are usually within the normal range, but severe hyperthyroidism may occur (7,10).

HCG-induced gestational hyperthyroidism without an underlying neoplastic process is typically limited to the first trimester and, if required, it can be managed with standard antithyroid medications (3,4). Propylthiouracil is the preferred drug because of lower transplacental

transfer and of greater experience with its use in pregnancy. Of note, gestational hyperthyroidism is frequently associated with hyperemesis gravidarum (3,4,17,18). It has been proposed that the hyperemesis may be related to a marked hCG-induced increase in estradiol levels (19). However, the relation between hyperemesis and gestational hyperthyroidism varies widely among patients and additional, unidentified mechanisms may be involved.

In patients with paraneoplastic hCG-secretion, the primary therapy consists of surgical removal of hydatiform moles, and in the case of choriocarcinomas of chemotherapy (7). Multimodality therapy with combination chemotherapy employing etoposide, high-dose methotrexate, actinomycin D, cyclophosphamide and vincristine and adjuvant radiotherapy and surgery, when indicated, has resulted in cure rates of 80-90% in patients with high-risk metastatic gestational trophoblastic tumors. However, 25-30% of high-risk patients will have an incomplete response to first-line chemotherapy or will relapse from remission. Salvage chemotherapy with cisplatin/etoposide, usually in conjunction with bleomycin or ifosfamide, as well as surgical resection of sites of resistant disease in selected patients, will result in a cure for most patients (20).

Symptomatic hyperthyroidism can be treated with beta receptor antagonists and/or thyreostatic drugs. Cure of the tumor will result in treatment of the hyperthyroid state, as illustrated by this patient who had subclinical hyperthyroidism caused by a metastatic choriocarcinoma with unusually high levels of hCG. She responded rapidly to a chemotherapeutic regimen with etoposide, methotrexate and dactinomycine, and six months after initiation of therapy, she is in complete remission.

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