Choriocarcinoma-induced thyrotoxicosis: Report of a case and review of the literature

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Unusual forms of thyrotoxicosis include gestational trophoblastic disease. Clinical evidence of thyrotoxicosis accompanied by a pelvic mass and a β -subunit of hCG elevated beyond the expected gestational age should make one suspect for this clinical entity. A patient presented with these features. Therapeutic intervention and discussion of this clinical entity is presented.

Unusual forms of hyperthyroidism include thyrotoxicosis factitia, hypersecretion of pituitary thyrotropin secondary to adenoma, iodine-induced hyperthyroidism, and thyrotoxicosis associated with gestational trophoblastic disease (GTD), including hydatidiform mole and choriocarcinoma.¹ To our knowledge, the first case of hydatidiform mole with thyrotoxicosis was reported in 1955 by Tisne and colleagues.² Since then, several cases of GTD-induced hyperthyroidism have been documented.³⁻⁸

We present an additional case and review the clinical and chemical manifestations of the disease.

Report of case

A 17-year-old girl was admitted with nausea, vomiting, anorexia, and a 15-pound weight loss of one month's duration. Two weeks prior to hospitalization, she had noted the onset of jaundice.

The patient denied a past history of hepatitis, recent transfusions, or intravenous drug use, as well as thyroid disease, heat intolerance, diarrhea, or iodide ingestion. She did report an episode of pelvic inflammatory disease. Her last menstrual period had been one month prior to admission. The family history included diabetes mellitus and thyrotoxicosis; however, the nature of these problems could not be elicited.

The pulse rate was 110 beats per minute and regular, the respiration rate was 20 per minute and regular, and the temperature was 98.6°F. The patient's skin was smooth, pale, and icteric. She had a biocular stare with tremor of the closed eyelids, but without bilateral lid retraction or infiltrative exophthalmos. Neck examination revealed a nontender, palpable thyroid gland without bruit; there was no evidence of supraclavicular or submandibular lymphadenopathy.

Cardiovascular review elicited accentuated S₁ and S₂ sounds and no S₃ or S₄ sounds. No Means-Lerman click was heard. The lung fields were clear to auscultation. A firm mass in the right lower quadrant was painful on palpation. There was no evidence of hepatomegaly or splenomegaly. Bowel sounds were audible in all quadrants.

The complete blood count disclosed hemoglobin and hematocrit values of 10.7 g/dL and 32.6%, respectively; the WBC count was 11,800/ μ L. Other significant laboratory values were as follows: LDH, 588 U/L; serum alkaline phosphatase, 164 U/L; alanine aminotransferase (ALT), 23 U/L; aspartate aminotransferase (AST), 40 U/L; total bilirubin, 6.9 mg/dL; direct bilirubin, 4.0 mg/dL; and indirect bilirubin, 1.8 mg/dL. T₃ and T₄ radioimmunoassay values were 399 ng/mL and 28.4 μ g/dL, respectively. The T₃ resin uptake was 29%, and the free thyroxine index was 3.5 ng/dL. The hCG β -subunit titer was 861 mIU/mL. (Normal are 20 mIU/mL 3 weeks after the last menstrual period, 350 mIU/mL 4 weeks following the last menstrual period, and 23,000 mIU/mL 5 weeks after the last menstrual period.)

Chest roentgenography demonstrated no evidence of cardiac enlargement, with clear costophrenic angles, and no evidence of infiltrates. The 24-hour iodine 123 uptake and thyroid scan with 100 μ Ci of ¹²³I revealed a uniformly enlarged thyroid gland with a 55% 24-hour uptake. This was consistent with thyrotoxicosis. A liver and spleen scan was performed with approximately 4 μ Ci of technetium sulfur-colloid, which revealed no filling defects.

Fig 1. Ultrasonic demonstration of a huge mass of variously sized cystic lesions emanating out of the pelvis and extending up into the left upper quadrant of the abdomen.

Fig 2. β -Subunit titers of hCG, as measured on the 46th, 50th, 54th, 57th, 64th, 69th, and 72nd days after the last menstrual period, are seen to decrease following chemotherapy for choriocarcinoma.

Pelvic ultrasonography revealed a large mass within the abdomen on the right (Fig 1). The tumor, which measured $9.4 \times 11.2 \times 17$ cm and which was predominantly solid, with an irregular cystic lumen, was thought to be a necrotic neoplasm. Bilateral hydronephrosis also was visualized.

The patient's hospital course included hydration, transfusions, propranolol (10 mg every six hours), and propylthiouracil (200 mg every six hours). She was transferred to another institution for further diagnostic and therapeutic intervention. Subsequent hepatic angiogra-

phy revealed multiple hepatic hypervascular loci, which were consistent with a diagnosis of metastatic choriocarcinoma. Dilatation and evacuation revealed no trophoblastic tissue.

The patient's chemotherapeutic course included methotrexate, actinomycin D, and cytosin. She also received radiation therapy to the pelvis (a total of 1,600 rads, in eight fractions of 200 rads).

One month following the start of the combined therapy, thyroid function values reverted to normal (T_3 and T_4 radioimmunoassays, 163 ng/dL and 7.3 μ g/dL, respec-

tively; free thyroxine index, 5.7 ng/dL). The hCG β -subunit titer had decreased consistently, as well (Fig 2).

Discussion

Trophoblastic-induced thyrotoxicosis is now considered to be a spectrum of clinical conditions, which range from subclinical chemical hyperthyroidism to clinical and chemical hyperthyroidism.⁹ The specific prevalence of this entity is not known, perhaps because of its varied presentation. Whether it is hydatidiform mole or choriocarcinoma, GTD more commonly persists with covert than with overt thyrotoxicosis disease.^{4,8,10,11}

In their series of 20 patients with gestational trophoblastic neoplasia, Nisula and Taliadouros³ noted three with covert hyperthyroidism, two with overt hyperthyroidism, and 15 with normal thyroid function. Odell and associates⁷ reported seven patients with covert hyperthyroidism in their series of 93 patients with metastatic trophoblastic disease. Miyai and coworkers⁸ and Dowling and associates¹⁰ also reported patients with GTD-associated covert thyrotoxicosis. The reason for the higher incidence of covert disease is not apparent, but it may be related to the duration of disease. Patients may develop overt hyperthyroidism following a prior asymptomatic course.

The glycoproteins thyroid-stimulating hormone (TSH) and hCG contain α -subunits and β -subunits. The α -subunit of hCG is homologous with other gonadotropins; the β -subunits differ, but they have considerable homology in their amino acid sequences. There is general agreement that a thyroid-stimulating factor secreted by the trophoblastic tumor is responsible for the increased thyroid function in patients with GTD.³ However, the nature of this process remains undefined.

Nisula and Taliadouros,³ using a mouse bioassay, examined urine and serum for thyroid-stimulating activity from 20 patients with trophoblastic neoplasia. Their findings demonstrated a direct correlation between thyroid-stimulating activity and hCG that suggested a qualitative similarity. Quantitative levels of hCG obtained from serum and urine samples with thyroid-stimulating activity exceeded 2,000 mIU/ml. Because no other thyroid-stimulating factor was apparent in this study, the causative agent of the thyrotoxicosis was concluded to be hCG, both quantitatively and qualitatively.

Cave and colleagues¹² examined serum from a patient with metastatic choriocarcinoma. By utilizing gel filtration, a single peak coinciding with hCG was demonstrated. This suggested that the thyrotropin of choriocarcinoma was hCG. Although 1 unit of hCG from Cave's patients had an immunologic activity of 1.16 units of bovine TSH, the

extremely high levels of hCG may explain the thyrotoxicosis adequately. Using a crude extract of hCG, Silverberg and associates¹³ demonstrated hCG biologic activation of adenylate cyclase in human thyroid tissue slices.

Our patient developed manifestations of thyrotoxicosis and had higher hCG titers than would be expected for gestational age. However, following uterine evacuation and combined chemotherapy and radiation for choriocarcinoma, there was a substantial reduction in hCG titer. This decrease in thyroid-stimulating activity resulted in a substantial improvement in the clinical symptoms of hyperthyroidism.

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