Choriogonadotropin-Mediated Thyrotoxicosis in a Man

Heather J. Cain,¹ Peter R. Pannall,¹ Dusan Kotasek,² and Robert J. Norman³

A 38-year-old man with a metastatic gonadotropin-secreting tumor of unknown primary origin presented with both clinical and biochemical findings of hyperthyroidism in association with markedly increased concentrations of human choriogonadotropin (hCG) in plasma. After chemotherapy, the concentrations of both hCG and free thyroxin decreased and the patient became euthyroid. We discuss the rare occurrence of this presumably hCG-driven hyperthyroidism in men and compare it with the relatively more common euthyroid hyperthyroidism associated with choriocarcinoma in women.

Additional Keyphrases: cancer · hyperthyroidism · gonadotropin-secreting teratocarcinoma · sex-related differences

The association between hyperthyroidism and trophoblastic disease is well recognized as one of the endocrine syndromes resulting from the production of polypeptide hormones by tumors. This association between very high concentrations of human choriogonadotropin (hCG) in serum of women with trophoblastic disease and hyperthyroidism is well documented (1–3). However, the association in men is rare. Despite considerable research into this area, the thyroid stimulator has not been definitively identified. Many believe it to be hCG, but multiple reports in the literature both confirm and refute hCG as the thyroid stimulator (2–6).

hCG is a glycoprotein hormone (molecular mass, 39 500 Da) consisting of an alpha and a beta subunit, very similar in structure to thyrotropin (thyroid-stimulating hormone; TSH), and is known to bind to the TSH receptor and generate cyclic adenosine 3’, 5’-monophosphate (cAMP) (7–10). As with many other glycoproteins, hCG is heterogeneous in biological fluids. These variant forms of hCG are believed to result mainly from differences in the sialic acid content of the molecule; however, variations in its protein core also produce different molecular forms of hCG (11).

We describe the case of a man with thyrotoxicosis believed to be secondary to stimulation of TSH receptors by hCG. The hCG was a tumor product, the majority of which was intact and very acidic.

Case Report

A 38-year-old man presented in August 1989 with a two-week history of swelling of the left side of his neck and a six-month history of lethargy. There was no unusual past medical or family history except for untreated mild hypertension and a 20-pack-year smoking history.

Examination showed a fixed 2-cm nodal mass in the left lower cervical area but no other abnormal findings. A fine-needle aspirate indicated the presence of a pleomorphic, poorly differentiated carcinoma. Histopathology of tissue obtained at open biopsy showed total replacement of the node by poorly differentiated, pleomorphic carcinoma with numerous mitotic figures and central areas of necrosis. Histochemical stains were positive for epithelial membrane antigen and the beta subunit of hCG, but were negative for S100, a marker for malignant melanoma (Figure 1). Serum hCG measured at the time of surgery was 870 000 int. units/L [in terms of the 1st International Reference Preparation (IRP) of hCG], alpha-fetoprotein was <3 kilo-int. units/L (reference interval <11), and carcinoembryonic antigen was 2.6 µg/L (reference interval <10). A presumptive diagnosis of teratocarcinoma was made; the primary site was not identified.

When seen one week later, the patient complained of rapid growth of the left neck mass, cough, dyspnea, and intermittent weakness and sensory disturbances affecting the left side of his body and face. Examination showed the patient to be slightly breathless with a large 5 x 3 cm fixed mass in the left lower cervical and supraclavicular area. Horner’s syndrome on the left side, and left-sided pyramidal tract signs involving both the upper and lower limbs. His blood pressure was 170/95 mmHg and his pulse rate was 87/min. We found

Fig. 1. Left cervical node biopsy: [220× magnification with immunoperoxidase staining showing hCG in the tumor cells]

Departments of ¹ Clinical Chemistry and ²Haematology-Oncology, and ³ Reproductive Medicine Unit Laboratory, Department of Obstetrics and Gynaecology, University of Adelaide, The Queen Elizabeth Hospital, Woodville, South Australia, 5011.

*Nonstandard abbreviations: hCG, human choriogonadotropin; TSH, thyrotropin (thyroid-stimulating hormone); cAMP, cyclic adenosine 3’5’-monophosphate; CT, computed tomography; IRP, International Reference Preparation; and FT₄, free thyroxin.

Received February 4, 1991; accepted March 28, 1991.
no adenopathy in other areas; the liver and spleen were not palpable and the testes were clinically normal. There was no documented thyroid gland enlargement or gynecomastia, and no lid lag, exophthalmos, or bilateral proximal myopathy. The remainder of the physical examination was within normal limits.

A chest roentgenogram showed multiple cannonball metastases throughout both lung fields. These were confirmed with a computed tomographic (CT) scan of the chest, which also showed no evidence of a mediastinal mass or adenopathy. CT scan of the brain revealed three hemorrhagic opacities in the cerebrum with considerable surrounding edema consistent with metastases. CT scan of the abdomen showed no evidence of abdominal visceral or nodal metastases, and all pelvic structures were normal. Ultrasound of both testes was normal. A complete blood series showed a leukocytosis (25 × 10⁹/L) with neutrophils 76%, lymphocytes 12%, monocytes 9%, eosinophils 1%, metamyelocytes 2%, and myelocytes 1%. Alkaline phosphatase (EC 3.1.3.1) activity was 255 U/L (reference interval: 35–115 U/L), γ-glutamyltransferase (EC 2.3.2.2) 194 U/L (5–60 U/L), lactate dehydrogenase (EC 1.1.1.27) 1326 U/L (120–250 U/L), and alanine aminotransferase (EC 2.6.1.2) 95 U/L (0–45 U/L).

The patient was given oral dexamethasone to combat the cerebral edema, and, after bulk harvesting of bone marrow, was started on intravenous chemotherapy for nonseminomatous germ cell tumors: etoposide (100 mg/m², days 1–5), cisplatin (20 mg/m², days 1–5), and bleomycin (30 units on day 2).

Within 48 h of starting chemotherapy, the patient’s respiratory symptoms worsened, with fevers, marked hemoptysis, dyspnea, and hypoxemia. The chest roentgenogram revealed diffuse interstitial opacities and we made a presumptive diagnosis of acute bleomycin-induced lung injury. The patient’s condition deteriorated and he was admitted to the intensive care unit. His course there was complicated by worsening left-sided paralys, prolonged neutopenia and thrombocytopenia, polymicrobial sepsis, and infectious esophagitis. He required intubation, mechanical ventilation, and a brief course of hemodialysis for acute tubular necrosis. Multiple episodes of supraventricular tachycardia, labile hypertension, and tachycardia were also noted during this time. This prompted evaluation of the patient’s thyroid status, which was difficult to assess clinically because of the many confounding factors. Thyroid-function tests at this time confirmed the clinical suspicion of hyperthyroidism (Table 1).

After completing the second cycle of chemotherapy, the patient declined all further treatment. He died one month later after returning home. No postmortem was performed.

**Materials and Methods**

We measured the serum concentrations of free thyroxin (fT₄), total triiodothyronine, and thyroxin-binding globulin by using the respective Amerlite assay kits (Amersham International, Amersham, Bucks., U.K.).

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Reference interval*</th>
</tr>
</thead>
<tbody>
<tr>
<td>fT₄, pmol/L</td>
<td>&gt;95</td>
<td>10–25</td>
</tr>
<tr>
<td>TSH, milli-int. units/L</td>
<td>0.2</td>
<td>0.2–2.9</td>
</tr>
<tr>
<td>Total T₄, nmol/L</td>
<td>&gt;218</td>
<td>60–140</td>
</tr>
<tr>
<td>Total T₃, nmol/L</td>
<td>3.2</td>
<td>1.1–2.3</td>
</tr>
<tr>
<td>TBG, mg/L</td>
<td>17</td>
<td>10–33</td>
</tr>
<tr>
<td>hCG, int. units/L</td>
<td>1.54 × 10⁴</td>
<td>&lt;4</td>
</tr>
<tr>
<td>Estradiol, pmol/L</td>
<td>2730</td>
<td>&lt;110</td>
</tr>
<tr>
<td>TSI</td>
<td>nd</td>
<td></td>
</tr>
</tbody>
</table>

*In-house values.*

T₄, triiodothyronine; TBG, thyroxin-binding globulin; T₄, thyroxin; TSI, thyroid-stimulating immunoglobulin; nd, not detected.

These methods are competitive immunoassays based on enhanced luminescence. fT₄ is measured by an analog technique and one cannot, by dilution, reliably measure concentrations >95 pmol/L.

We measured the TSH in serum with the Amerlite TSH-60 assay kit (Amersham), an immunometric technique based on enhanced luminescence. The lower limit of detection is 0.1 milli-unit/L. According to the manufacturer, hCG at 250 000 int. units/L has no detectable cross-reaction in this assay system.

Serum hCG was measured with the hCG Mabilaclone assay kit (Serono Diagnostics, Woking, Surrey, U.K.). An immunoradiometric technique with magnetic solid-phase separation, this method recognizes both the intact hCG molecule and free beta chains. The method is standardized against the 1st IRP and the 3rd International Standard 75/537. The free beta subunit of hCG was measured by a specific immunoradiometric assay after chromatography (12). The intra- and interassay coefficient of variation for all these assays is <10%.

Thyroid-stimulating immunoglobulin was measured by using an in vitro bioassay based on the release of cAMP from isolated human thyroid cells. Total thyroxin was measured by radioimmunoassay.

Serum samples, one from the patient with presumed gonadotropin-secreting metastatic teratocarcinoma and another from a woman at nine weeks of pregnancy, were subjected to gel filtration on a 35.4 × 2.6 cm Sephacryl 200 column (Pharmacia, Uppsala, Sweden), pre-equilibrated and eluted with 50 mmol/L ammonium acetate buffer (pH 7.4) at a flow rate of 0.25 mL/min. We collected 1-mL fractions and analyzed them for hCG, using an immunoradiometric assay specific for intact hCG as described previously (12). Fractions that showed hCG immunoactivity were pooled, desalted, and concentrated in a stirred cell membrane-filtration unit (Amicon, Inc., Danvers, MA) with an M₃, 1000 cut-off membrane. Part of the concentrate was subjected to chromatofocusing on a Mono P HRS/20 column (Pharmacia) that had been equilibrated with piperazine buffer (20 mmol/L, pH 6.3). The pH gradient was formed by eluting with Polybuffer® 74 (Pharmacia), diluted 10-fold with water and acidified to pH 3.5 with HCl. After 1.0 mL of the eluting buffer had been pumped through the
column, we loaded 50 μL of the above concentrate onto the column. The flow rate was 0.4 mL/min. The pH was monitored by using an in-line flow-through pH electrode (Pharmacia) connected to a chart recorder, and 0.5-mL fractions were collected into tubes holding 0.2 mL of phosphate buffer (50 mmol/L, pH 7.4) containing 0.15 mol of NaCl, 5 g of bovine serum albumin, and 2 g of sodium azide per liter. The fractions were assayed for hCG immunoradiometrically, as described above.

**Results**

Once the diagnosis of hyperthyroidism was confirmed, previous and subsequent samples were analyzed for fT4 and hCG. The results are shown in Figure 2.

Gel chromatography showed the predominant molecular species of hCG to be the intact molecule. The quantity of free beta subunits was greater than that in a reference preparation of pregnancy serum (Figure 3). With chromatofocusing, the intact hCG showed significantly more acidic variants than did the pregnancy specimen (Figure 4). The peaks were eluted at pI 3.85, 4.15, 4.3, 4.5, and 4.75, the latter two being considerably smaller than in the pregnancy hCG sample.

**Discussion**

Hyperthyroidism in men with hCG-secreting tumors, first described by Steigbigel et al. in 1964 (13), was reviewed by Marechaud et al. (14) in 1985, who summarized four reported cases (13, 15–17) and added a fifth. We searched the literature and identified three additional cases involving men (10, 18). All had either extensive choriocarcinoma or embryonal carcinoma. Our patient had metastatic poorly differentiated carcinoma, which, for treatment purposes, was presumed to be a teratocarcinoma. The primary site was never identified.

The signs of hyperthyroidism in these patients are often masked by features of the accompanying malignancy. Tachycardia is usually present, and tremor, lid retraction, and proximal myopathy have also been noted. In our patient, only tachycardia was evident. Gynecomastia was documented in all cases reviewed, but was not noted in this case, which is surprising given his very high concentrations of estrogen.

The natural history of hyperthyroidism in women with trophoblastic disease, as shown by Norman et al. (3), is the development of biochemical hyperthyroidism preceding the clinical manifestations of thyrotoxicosis. In their series of women patients, biochemical evidence of hyperthyroidism was usually present at plasma concentrations of hCG >100 000 int. units/L (2nd International Standard) and clinical toxicity was present at concentrations >300 000 int. units/L. This progression is well illustrated in our case, with retrospective analysis showing the fT4 to be marginally above normal on presentation and increasing to toxic concentrations before the start of chemotherapy.

This natural progression has been less clearly documented in men. In a separate paper, Norman et al. (4) reported on six male patients with testicular tumors that produced concentrations of plasma hCG ranging...
can bind and activate thyroid tissue in vitro (7–10). In studies by Mann et al. (10), the acidic variants of hCG (pI 3.6–3.8) showed dose-dependent stimulation of triiodothyronine release and cAMP generation from human thyroid slices, whereas other hCG fractions had no thyrotropic activity at similar doses. These findings strongly suggest that the acidic variants can act as stimulators of human thyroid tissue in vitro. Isoelectric focusing of serum from patients with trophoblastic tumors reveals substantial amounts of the acidic isoelectric variants (pI 3.3–3.9), whereas these variants are barely detectable in normal pregnancy. Cassels et al. (19) published data indicating that the acidic variants of hCG have a delayed clearance, which contributes to the increased proportion of acidic variants of hCG in the serum of patients with hCG-producing malignancy after treatment. As previously stated, acidic isoelectric variants accounted for almost all of the hCG in our patient. This dependence on form as well as concentration may account for the variable appearance of hyperthyroidism in patients with very high concentrations of hCG. What is unexplained, however, is the lack of effect of the serum on human thyroid cells in vitro in testing for thyroid-stimulating immunoglobulin activity in this patient. Clearly, no thyroid-stimulating immunoglobulin was present, but we did expect that hCG in the specimen would have stimulated cAMP release from the cells.

In conclusion, the exact nature of the thyroid stimulator in trophoblastic disease remains unknown, but we assume it is hCG. The lack of thyroid abnormalities in men with very high concentrations of hCG has led some to doubt that hCG is the thyroid stimulator. Perhaps the heterogeneity of circulating hCG has lead to the discrepancies in studies of thyrotropic activity of hCG. hCG components have been identified that exist almost exclusively in patients with trophoblastic disease; generally, these are acidic, highly sialated variants of hCG. Perhaps the thyrotropic stimulatory activity is linked to a small concentration range of acidic hCG variants.

We thank Mr. Fred Amato for technical assistance and Dr. Peter Ward, Royal North Shore Hospital, New South Wales, for thyroid-stimulating immunoglobulin analysis.

References


