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CLINICAL CASE SEMINAR

Sudden Enlargement of Local Recurrent Thyroid Tumor after Recombinant Human TSH Administration

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Chronic endogenous TSH stimulation of neoplastic tissue has been reported to stimulate tumor enlargement. However, little is known about changes in normal and neoplastic thyroid tissue after sudden rather than chronic stimulation with TSH. Acute thyroidal tissue reactions, reflected by rapid tumor expansion and/or possible vascular changes, have been reported to occur after bovine TSH stimulation and, more recently, after recombinant human TSH (rhTSH).

In this report, we describe two patients with papillary thyroid carcinoma with local recurrent tumor. Both patients developed tumor growth 12–48 h after the second rhTSH injection, reflected by acute respiratory distress or a palpable, tender mass. In both situations, the enlargement was documented by imaging techniques, showing tumor expansion compared with previous examinations. Rapid improvement with glucocorticoid supports inflammation as the likely etiology. Based on these cases, and other reports of rapid tumor expansion after rhTSH injection, we recommend glucocorticoid coverage before rhTSH administration for patients with known or suspected neoplasia located in a limited space. (*J Clin Endocrinol Metab* 86: 5148–5151, 2001)

LEVOTHYROXINE (L-T_4) WITHDRAWAL is being increasingly replaced by recombinant human TSH (rhTSH) for follow-up radiodine scanning of patients with differentiated thyroid cancer. In previous studies (phases I/II and IIIa) (1, 2), rhTSH was shown to effectively stimulate ^{131}I uptake in the remnant thyroid tissue and in tumor metastases. A multicenter study with 220 patients with papillary or follicular thyroid cancer demonstrated rhTSH to be as sensitive as L-T_4 withdrawal when combined with thyroglobulin measurement in the detection of thyroid remnants and distant metastases (3). Patients who received rhTSH did not experience hypothyroid symptoms and were reported to maintain a good quality of life.

rhTSH has been advocated in patients with brain or spinal metastases to avoid chronic endogenous TSH stimulation of neoplastic tissue, which could predispose to tumor expansion (2, 3). However, adverse reactions likely due to tissue stimulation following rhTSH administration have been reported. Hemiplegia due to hemorrhage in a brain metastasis (4) and bone pain at a metastatic site (5) have been described after rhTSH injection.

We herein describe two patients with papillary carcinoma in whom rhTSH injection resulted in sudden enlargement of cervical tumor mass causing partial tracheal obstruction.

Patients and Methods

Case descriptions

Case 1. An 80-yr-old woman presented in April 1995 with a 1-wk history of enlargement of the thyroid gland. Physical examination was unremarkable except for a 3 × 3 cm firm mass in the right thyroid lobe causing tracheal displacement to the left. No cervical lymph nodes were palpable. A fine needle aspiration biopsy performed on the palpable mass revealed papillary carcinoma.

In May 1995, a total thyroidectomy was performed. A 4-cm tumor in the right lobe of the thyroid, firmly attached to the larynx, the trachea, and the esophagus, and infiltrating adjacent muscles and laryngeal nerve, was removed. The tumor was resected off the larynx, trachea, and esophagus by eletrocautery, but all neoplastic tissue could not be completely removed. Histologically, the tumor was characterized as tall cell variant of papillary thyroid carcinoma with focal infiltration into the skeletal muscle. Following surgery, the patient developed asymptomatic hypocalcemia that was stabilized before discharge with oral calcium supplements and vitamin D.

After surgery, the patient was started on T_3 replacement, on which her serum TSH was 0.12 mU/liter and serum thyroglobulin 308 ng/ml. In June 1995, 3700 megabecquerels (MBq) [100 millicuries (mCi)] of radioactive iodine was administered after which the patient was started on levothyroxine suppression therapy with 0.112 mg/d. The post therapy whole body scan (WBS) showed significant uptake limited to the thyroid bed. During levothyroxine suppression therapy, her serum TSH was <0.03 mU/liter and serum thyroglobulin was 44.2 ng/ml. In February 1996, a diagnostic WBS showed persistent uptake in the thyroid bed. A second dose of 5550 MBq (150 mCi) ^{131}I was administered. The post-therapy WBS again revealed the uptake in the thyroid bed without distant metastases. In October 1996, her serum thyroglobulin was 82.6 ng/ml on L-T_4 suppression (serum TSH = 0.087 mU/liter). On L-T_4 withdrawal in November 1996 (serum TSH = 82.1 mU/liter), serum thyroglobulin rose to 1,855 ng/ml. A diagnostic WBS was negative, but, due to the elevated serum thyroglobulin levels, a third dose of ^{131}I (7400 MBq, 200 mCi) was administered. The post therapy WBS showed minimal uptake in the area of the thyroid bed. In February 1997, a neck ultrasound was performed which showed no evidence of thyroid tissue. A computed tomography (CT) scan of the neck showed a soft tissue density in the right hypopharynx with possible erosion of the right thyroid cartilage. In March 1998, an ultrasound of the neck was again unremarkable, and a repeat CT scan now showed no definite evidence

Abbreviations: bTSH, Bovine TSH; CT, computed tomography; L-T_4, levothyroxine; MRI, magnetic resonance imaging; rhTSH, recombinant human TSH; WBS, whole body scan.

of a mass in the neck and a normal trachea. In July 1998, the serum thyroglobulin was 191 ng/ml and serum TSH was 0.004 mU/liter. Antithyroglobulin antibody measurements were repeatedly negative.

In July 1999, the patient noted intermittent dysphagia and a neck ultrasound showed a soft tissue mass measuring 2.1 × 1.1 × 1.7 cm in the right neck. An ultrasound-guided fine needle aspiration biopsy showed recurrence of the papillary carcinoma. In September 1999, while on L-T_4 suppression (TSH = 0.002 mU/ml), thyroglobulin levels had risen to 225 ng/ml. Because the patient had previously become depressed and severely debilitated following L-T_4 withdrawal, consideration was given to possible therapy with rhTSH. In preparation for a WBS, rhTSH (Thyrogen, Genzyme Transgenics Corp., Cambridge, MA) was administered (0.9 mg im for 2 d) on November 29 and 30, 1999. On the afternoon after the second injection, the patient developed right neck pain radiating to the ear that persisted until the following day. On December 2, approximately at 0100 h, she suddenly awakened with shortness of breath and noted a peculiar sound when she inspired. On physical examination in the Sinai Hospital Emergency Room, the patient was found to be stridorous, but there was no evidence of rash or swelling of the tongue, lips, or face. Routine laboratory studies were normal. There was no eosinophilia and the serum TSH was 216 mU/liter, reflecting the rhTSH administration. Because this was considered to be a possible allergic reaction to rhTSH, she was started on a racemic epinephrine nebulizer and 60 mg iv hydrocortisone q8 h, resulting in rapid improvement of her stridor. A soft tissue x-ray of the neck showed a mass deviating the trachea to the left at the level of C5-C6, and a neck ultrasound again showed a 2.2-cm mass in the right thyroid bed. On the following day, her physical examination was normal and she was discharged from the hospital. Seventy-two hours after the second injection, a 2.2-mCi ^{123}I WBS did not show any functioning thyroid tissue, although serum thyroglobulin was 8440 ng/ml. Three days following the second rhTSH injection, the patient still felt uncomfortable with inspiration. The next day, a CT scan of the neck showed a soft tissue mass, with some areas suggesting edema (Fig. 1), causing narrowing of the airway that had reappeared since the prior examination on February 1998. A repeat CT scan 20 d later showed reduction in the size of the soft tissue mass (Fig. 2).

In February 2000, surgery was performed to remove the mass because of mild but persistent dysphagia. On histological examination, only scar tissue with a microscopic focus of papillary carcinoma was seen. After surgery, the patient's symptoms of dysphagia resolved. In September 2000, a repeat ultrasound of the neck showed a lesion in the right thyroid bed measuring 1.3 × 1.0 × 0.9 cm, which was not confirmed by CT scan of the neck. Thyroglobulin levels were 113 ng/ml and antithyroglobulin antibody was negative. In November 2000, a PET scan showed two foci of increased uptake in the region of the right thyroid bed, compatible with recurrent/residual thyroid carcinoma. External beam radiotherapy (4600 Gy) was administered to the thyroid bed in the hopes of preventing further clinical recurrence of the disease.

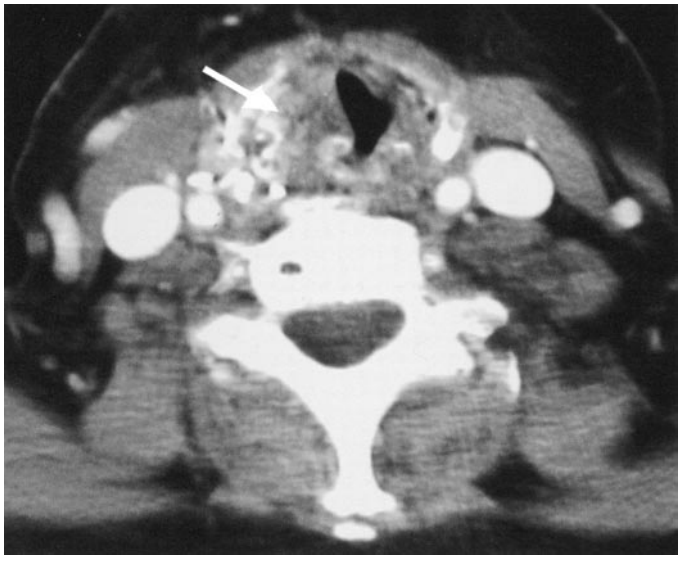

FIG. 1. Patient 1. CT scan of the neck 5 d after the acute episode showing tracheal compression by a mass on the *right*. Lower density inside the mass suggests edema (*arrow*).

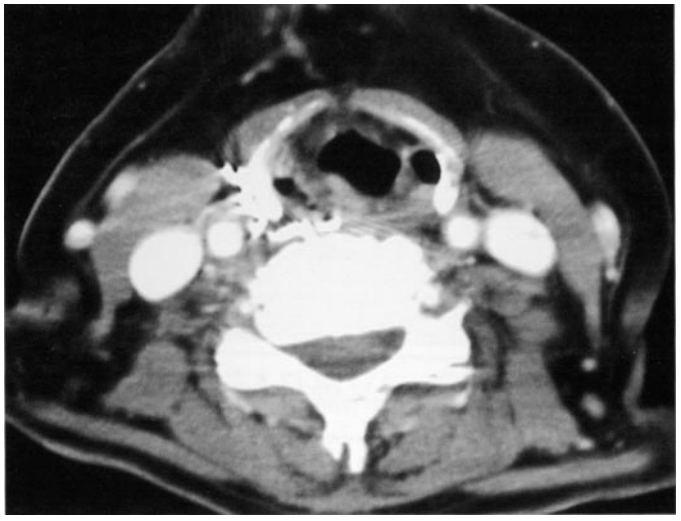

FIG. 2. Patient 1. CT scan of the neck 20 d after the episode showing reduction of tracheal compression.

Case 2. An 83-yr-old woman was diagnosed with papillary thyroid carcinoma 8 yr before referral in 1992, when she presented with an enlarging bilateral goiter. Total thyroidectomy was performed and surgical pathology revealed a 3.5-cm intrathyroidal follicular variant of papillary carcinoma with two other foci of micropapillary carcinoma. There was no extrathyroidal extension or lymph node metastases identified.

Following surgery, she was treated with 100 mCi of ^{131}I for anterior neck uptake noted on a 5 mCi ^{131}I scan. The patient was placed on L-T_4 suppression until she underwent a surveillance 5 mCi ^{131}I scan following T_4 withdrawal. The scan revealed no uptake in the neck or distant locations and she was placed back on L-T_4 suppression therapy. Thyroglobulin testing was not performed. She was subsequently managed without further imaging or other monitoring for thyroid cancer recurrence. She had no complaints of symptomatic thyrotoxicosis on L-T_4 and denied neck pain, dysphagia or dysphonia.

The patient's medical history is also significant for breast carcinoma treated with mastectomy in the 1970s without chemo or radiation therapy, myocardial infarction in 1986, and chronic stable angina with reduced left ventricular cardiac function, and edema.

At the time of initial evaluation in September 2000, the patient was receiving 0.088 mg of L-T_4 daily, hydrochlorothiazide, diltiazem, and atorvastatin. Physical examination revealed a healed thyroidectomy scar with no palpable thyroid tissue or adenopathy. There was a grade 2/6 systolic ejection murmur mild and nonpitting peripheral edema.

Laboratory data revealed a TSH of 0.382 mU/liter (0.5–4.5 mU/liter), free T_4 of 1.2 ng/dl (0.9–1.9 ng/dl), and a serum thyroglobulin level of 20.4 ng/ml. Magnetic resonance imaging (MRI) of the neck performed in October 2000 showed a node/thyroid bed lesion (Fig. 3). A neck ultrasound revealed a 1.2 × 1.4-cm mass in the lower right thyroid bed. Fine needle aspiration under ultrasound guidance revealed papillary thyroid carcinoma. Helical chest CT performed without contrast revealed no evidence of pulmonary metastases.

After a long discussion with the patient regarding the risk and benefits of treatment, the patient, along with her family, felt uncomfortable not treating the recurrent tumor. In view of her co-morbid conditions, the patient was scheduled for an ^{131}I scan using rhTSH stimulation to determine the iodine avidity of the mass, with a plan for ^{131}I therapy if uptake was demonstrated. Following 2 wk of a low iodine diet, the patient received two im doses of 0.9 mg of rhTSH (Thyrogen). Approximately 12 h after administration of the second dose of rhTSH, the patient presented to the emergency room with right sided neck pain with dysphonia. On physical exam, the patient was afebrile, the neck was extremely tender, and a mass was now palpable. A neck MRI, performed

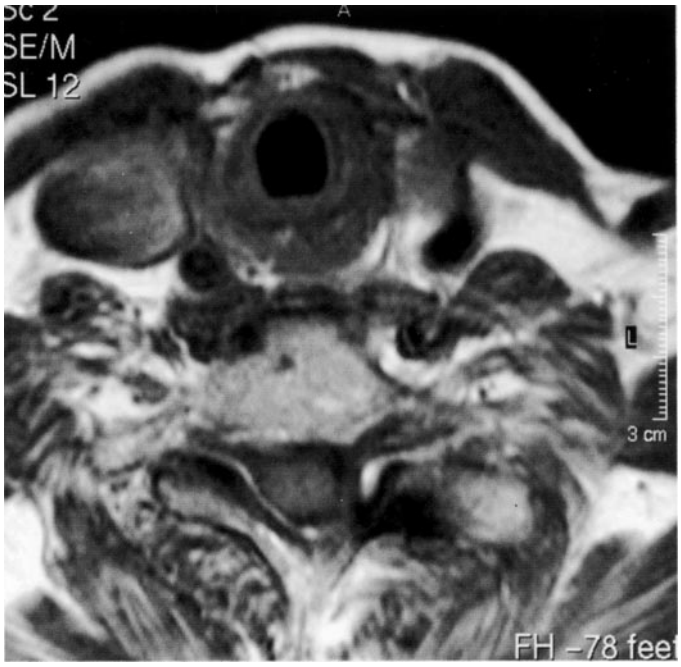

FIG. 3. Patient 2. MRI of the neck before rhTSH.

12 h after the second rhTSH dose, revealed a 30–50% enhancement and enlargement of the neck mass in comparison to the scan performed 12 wk earlier (Fig. 4). Indirect laryngoscopy revealed edema of the vocal cords with good movement bilaterally.

The patient was treated with one dose of iv methylprednisolone (60 mg) and was placed on a tapering dose of daily prednisone daily for the following 7 d. The pain subsided over the ensuing 24–48 h. Because she had received both doses of rhTSH, a 4-mCi ^{131}I WBS and stimulated thyroglobulin were performed. The ^{131}I scan revealed no uptake, but the thyrogobulin value stimulated to 797 ng/ml.

The patient was seen in follow-up 2 wk and then 8 wk after the scan and noted complete resolution of symptoms and disappearance of the palpable mass. She refused a follow-up neck MRI, but laboratory studies revealed a TSH of 0.41 with a serum thyroglobulin concentration of 4 ng/ml and no evidence of antithyroglobulin antibodies.

FIG. 4. Patient 2. MRI of the neck 12 h after rhTSH injection.

Results and Discussion

These cases illustrate rapid expansion of recurrent thyroid neoplasms after stimulation with rhTSH. The first patient had an aggressive variant of papillary thyroid carcinoma that was locally invasive and incompletely resected. A partial response to radioactive iodine therapy was seen as evidenced by a decrease in ^{131}I uptake in the thyroid bed. The second patient presented with a recurrent tumor after apparently complete resection of the thyroid. However, later there was probable dedifferentiation of the tumor in both patients reflected by the loss of ^{131}I uptake. Following rhTSH administration, there likely was an increase in the size of tumor mass, resulting in acute pain in the area of the tumor mass in both patients, respiratory distress in the first patient and dysphonia in the second patient. Rapid improvement with corticosteroid therapy suggested a likely inflammatory component of the tumor expansion. In the first patient, although the stridor subsided in a few hours, the patient continued to report difficulty in breathing for some days. A large tumor mass was not seen pathologically following surgery 3 months later, and it is likely, therefore, that the main tumor mass was incompletely resected, because residual tumor was seen on ultrasound, CT, and PET scan 6 months later. Allergic reactions like rashes or urticaria are uncommon after rhTSH (<1%) (6). In our patients, the absence of angioedema, rash, or eosinophilia during the acute episode makes the likelihood of allergic reaction to rhTSH very low.

Tumor expansion following L-T_4 withdrawal has been previously reported. This is of particular concern if the neoplastic tissue is located in a limited space where tumor expansion can compromise vital anatomic structures (7). For example, patients with known vertebral metastases have been reported to develop neurological symptoms due to spinal cord compression during thyroid hormone withdrawal in preparation for WBS. These symptoms resolved after L-T_4 was resumed (8). Chui *et al.* (9) described a patient with metastatic uptake in the brain who developed focal and motor weakness and severe headache during thyroid hormone withdrawal. This patient was treated with 200 mCi ^{131}I after resection of the two largest metastatic lesions and pretreatment with rhTSH and dexamethasone.

rhTSH has been used to stimulate radioiodine uptake for possible therapy on a compassionate need basis when either a patient's poor clinical condition precludes L-T_4 withdrawal, or when there is inability of the pituitary gland to provide a TSH response to hypothyroidism. According to the manufacturer, among 55 patients with CNS metastases who were enrolled in the rhTSH compassionate use protocol, 4 developed complications, including hemiparesis, hemiplegia, or headache after rhTSH injection, attributed to edema or focal hemorrhage within the tumor (6). One patient with metastasis to the optic nerve developed acute visual loss 24 h after rhTSH administration. Similar to our patient, severe dysphagia, secondary to laryngeal edema and requiring tracheotomy has been reported 24 h after rhTSH administration to a patient with metastasis to the paratracheal area (6). Vargas *et al.* (4) reported a hypopituitary patient with brain metastasis from follicular thyroid cancer who developed hemiplegia 24 h after the second rhTSH injection. On MRI, hemor-

rhage was seen within the tumor. Similarly, Robbins *et al.* (10) reported a patient with follicular carcinoma with multiple bone metastases who developed sudden onset of hemiparesis during L-T_4 withdrawal in preparation for a WBS. Imaging revealed a brain metastasis surrounded by edema that was subsequently resected. After the surgery, this patient received several rhTSH injections for the purpose of radioactive iodine ablation. Approximately 24 h after the second rhTSH injection, he developed confusion, ataxia, dysphagia, headache, and papilledema. On MRI, another brain mass surrounded by edema was seen. A recent report described two patients with bone metastases from thyroid cancer who developed transient swelling and pain at the metastatic site after rhTSH administration (5). Both patients reported the intensity of the pain to be the same as they had previously experienced during L-T_4 withdrawal, although it was shorter in duration. These cases suggest that rhTSH stimulation can lead to an acute response in neoplastic thyroid tissue.

The acute effect of rhTSH might have been anticipated from case reports of thyroid enlargement following injection of bovine TSH (bTSH) (11). For example, a 39-yr-old man developed sudden swelling of the thyroid gland accompanied by tenderness only 2 h after a second injection of bTSH (11). Eight hours following the injection, his thyroid grew in size from a baseline size of twice normal to six times the normal size. The thyroidal tenderness resolved spontaneously 72 h later. Similarly, a 22-yr-old female developed odynophagia with radiation to the ears along with a 2-fold enlargement of the thyroid gland 24 h after an injection of bTSH (11). The enlargement subsided after a few days. Even L-T_4 withdrawal has been reported to stimulate rapid tissue expansion. Maloof *et al.* described a 34-yr-old man with vertebral metastases who developed paraplegia only 4 d after a total thyroidectomy was performed (12). Because of these observations, caution has been recommended when rhTSH is used in patients with known or suspected CNS or vertebral metastases, and in such cases it would be prudent to give rhTSH with corticosteroid coverage (13, 14).

In our patients, a temporal relationship between the injection of rhTSH and the development of acute symptoms strongly suggests a direct effect of TSH on the development of inflammatory edema surrounding the tumor. Although the precise mechanism is not known, a vascular effect, followed by edema, has been proposed to be the mechanism responsible for acute tissue reactions after rhTSH stimulation (10). Doubling time of fetal human thyroid cell monolayers have been demonstrated to be reduced after addition of rhTSH, from 54 ± 2.1 to 31 ± 1.7 h, with a significant increase in cellular growth (15). However, a direct stimulation of neoplastic cell proliferation is less likely to have occurred in our patients, since symptoms developed within hours after rhTSH injection.

On the basis of the present cases and others, we strongly recommend caution when using rhTSH in patients with known or suspected metastases to the CNS and vertebra, and in patients with a large thyroid remnant or recurrent tumor in the neck. In such cases, adjunctive corticosteroid coverage should be considered. Luster *et al.* (16) administered dexamethasone 8 mg orally twice daily or prednisone 80 mg orally daily to prevent edema at the tumor site before rhTSH in patients with documented or clinically suspected brain or spinal cord metastases, with an uneventful outcome. This regimen was based on a routinely used protocol for patients with brain or spinal metastases receiving external beam therapy.

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