0021-972X/93/7604-1025$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 76, No. 4
Printed in U.S.A.

Thyrotropin-Producing Microadenoma Associated with Pituitary Resistance to Thyroid Hormone

KENJI WATANABE, TORU KAMEYA, AKIRA YAMAUCHI, NAOHITO YAMAMOTO, AKIRA KUWAYAMA, IZUMI TAKEI, HIROSHI MARUYAMA, AND TAKAO SARUTA

Department of Internal Medicine, Keio University School of Medicine, Tokyo 160; Department of Pathology, Kitasato University School of Medicine (T.K.), Kanagawa 228; Department of Neurosurgery, Kainan Hospital (N.Y.), Aichi 498; and Department of Neurosurgery, Nagoya University School of Medicine (A.K.), Nagoya 466 Japan

ABSTRACT

A 21-yr-old female with hyperthyroidism is described. Though her serum-free T_3 was 17.8 pmol/L and free T_4 was 60.2 pmol/L, TSH was as high as 10.7 mU/L. TRH stimulated an increase in TSH from 10.7–91.7 mU/L. T_3 administration in gradually increasing doses of 100, 200, and 400 mg/day resulted in gradual reduction in serum TSH. Cranial computed tomography and magnetic resonance imaging revealed a microadenoma of the pituitary gland. Histology of the surgical specimen showed a TSH-producing adenoma with TSH cell cluster islets and decreased numbers of TSH cells in the nonneoplastic pituitary. Cultured cells from the adenoma secreted TSH spontaneously and in response to TRH. This TRH-stimulated TSH secretion was suppressed by T_3 in a dose-dependent manner. One year postoperatively, neither residual tumor nor recurrence were seen by computed tomography and magnetic resonance imaging. However TSH, as well as free T_3 or T_4, was still high and overresponsive to TRH. (*J Clin Endocrinol Metab* **76:** 1025–1030, 1993)

PITUITARY thyrotroph (TSH) is usually suppressed in hyperthyroid patients (1). The syndrome of inappropriate secretion of TSH (IST) may be diagnosed in a patient if TSH is inappropriately elevated in the presence of elevated free serum thyroid hormones (2). The classification of IST depends on whether hypersecretion of TSH is associated with a neoplasm. TSH response to TRH or T_3 and the α/TSH molar ratio are thought to be important for differentiating these two types of IST (3, 4). In the present case, the hormone activities associated with an atypical TSH-producing adenoma are compatible with a diagnosis of nonneoplastic IST.

Case Report

A 21-yr-old female was admitted to our hospital because of goiter. She had noticed excessive sweating since 18 yr of age. On admission, she appeared well. Pulse rate was 120 beats/min. There was a fine tremor bilaterally. Thyroid gland was moderately swollen, soft, and movable. Her visual fields were normal. There was no sign of ophthalmopathy.

Laboratory examinations

Alkaline phosphatase, 449 IU/L; total cholesterol, 3.2 mmol/L. Ferritin was 15 μg/L. Sex hormone-binding globulin (SHBG) was 136 nmol/L (20–100 nmol/L). Serum osteocalcin was 8.5 μg/L (1.5–6.5 μg/L) and angiotensin-converting enzyme was 89 IU/L (18–44 IU/L).

Endocrinological examinations

Free T_3, 17.8 pmol/L; free T_4, 60.2 pmol/L; TSH, 10.7 mU/L; reverse T_3, 12.7 pmol/L; T_4-binding globulin, 218 nmol/L; and α-subunit, 1.7 μg/L (α/TSH molar ratio, 1.5). Basal ACTH, LH, FSH, PRL, and GH were normal. ACTH and cortisol reaction to 100 μg CRH were suppressed. GH reaction to 100 μg GHRH was also subnormal. LH and FSH reactions to 100 μg LH-releasing hormone were normal. Circulating anti-T_3 and anti-T_4 antibodies were negative using labeled T_3 and T_4 analogs (5, 6). Anti-TSH receptor antibody was negative. Antimicrosomal, antithyroglobulin, and antipituitary antibodies were also negative. Thyroid ^{123}I uptake was 51% at 3 h and 74% at 24 h. Thyroid scintigram by ^{123}I showed diffuse accumulation in the thyroid gland and slight enlargement. The basal metabolic rate was 30%.

Cranial computed tomography (CT) and magnetic resonance imaging (MRI) (Fig. 1) revealed a pituitary tumor and deviation of the stalk. The tumor size was 1.0 × 0.9 × 0.8 cm, and the tumor seemed to be homogeneous and restricted to the fossa. There were no findings of bony destruction. A transsphenoidal pituitary adenomectomy was performed. The tumor seemed to have been completely removed along with some normal pituitary tissue.

Although she appeared well and the goiter decreased in size after the operation, her heart rate was still over 100 beats/min and basic metabolic rate was 22%. One year after surgery, free T_3 (fT_3), free T_4 (fT_4), TSH, and α-subunit were 10.6 pmol/L, 47.4 pmol/L and 5.4 mU/L, and 0.4 μg/L, respectively (α/TSH molar ratio was 0.7). SHBG 130 nmol/L; ferritin, 7 μg/L; osteocalcin, 8.3 μg/L; and angiotensin-converting enzyme, 63 IU/L.

Subjects and Methods

Effect of exogenous T_3 on TSH response to TRH before the operation

Five hundred micrograms of TRH was administered iv before and after administration of oral T_3. For T_3, the dosage was increased every 3 days from 100–200–400 mg daily, given in split doses at 0800 and 2000 h. Serum TSH was measured before and 15, 30, 60, 90, 120, and 180 min after the TRH administration.

Histology, immunostaining, and electron microscopy

The surgical specimen was used for morphological studies. The tissue was fixed in 4% paraformaldehyde and 4% Bouin's fluid for 6 h,

Received December 31, 1991.
Address all correspondence and requests for reprints to: Izumi Takei, M.D., Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160 Japan.

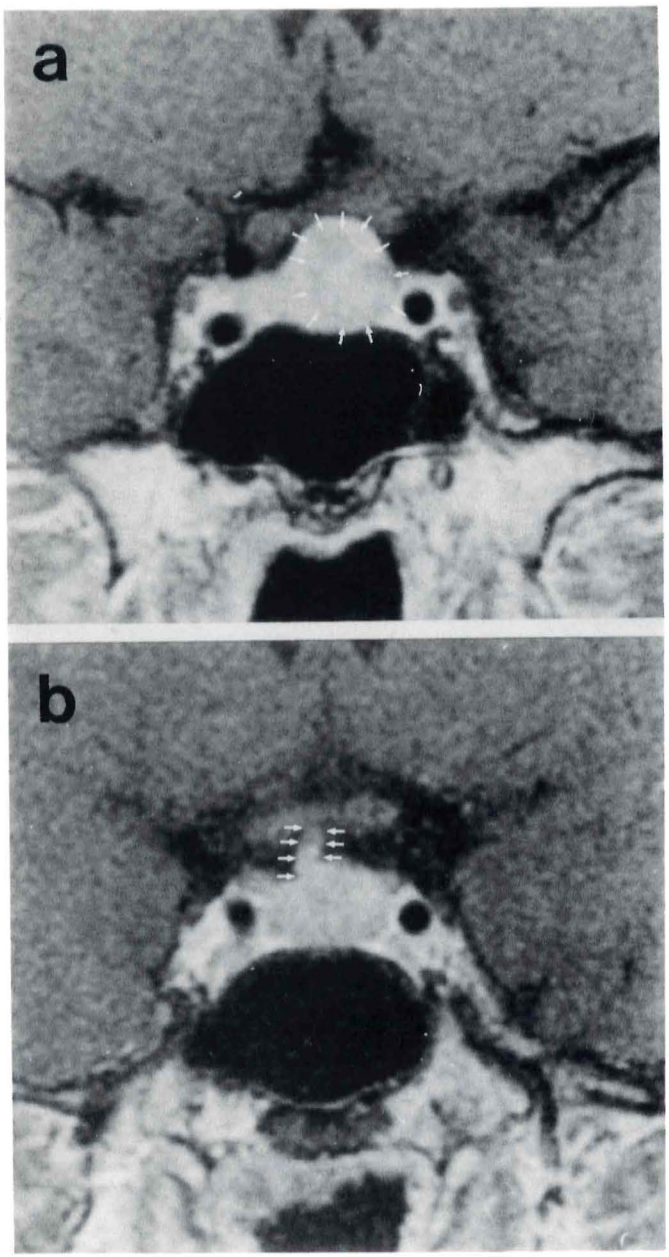

FIG. 1. Preoperative control T1-weighted spin-echo MRI. a, *Arrows* show a small round mass (1.0 × 0.9 × 0.8 cm) which is restricted in the sellar space; b, *arrows* show a deviation of the stalk.

dehydrated and embedded in paraffin for routine and immunohistochemical microscopy. In immunohistochemical staining for TSH, LH, FSH, PRL, GH, and ACTH, sections were incubated with antisera by the avidin-biotin-peroxidase complex (ABC) method (7). Antisera against TSH-β and FSH-β were preabsorbed with small amounts of purified FSH-β and TSH-β (donated by NIDDK, Bethesda, MD), respectively, to remove cross-contaminating antibodies (5–10 μg/μl 1000 × diluted antisera) (8). Antisera against TSH-β (AFP-37814624), FSH-β (AFP-3710194), α-subunit, LH, GH, and PRL were donated by Dr. A. F. Parlow (Pituitary Hormones Center, Harbor General Hospital, Torrance, CA) through the NIDDK. Antisera against ACTH was purchased from Immuno Nuclear, MN. Employing the ABC method, sections were incubated in the antisera (dilutions of 1:500 to 1:1000) for 30 min at room temperature or overnight at 4 C. Nontumorous pituitary sections were also incubated in each antiserum as positive controls.

For electron microscopy, adenomatous tissue was fixed in a mixture of 4% paraformaldehyde and 0.5% glutaraldehyde, buffered in phosphate at pH 7.2, using routine procedures.

Cell culture and effect of TRH on TSH secretion of tumor cells

The tissue was transported in a culture medium (Dulbecco's modified Eagle's medium (DMEM) (Nissui Pharmaceutical, Tokyo, Japan) containing 15% fetal calf serum (FCS) (Flow Laboratory, North Ryde, Australia) containing 1×10^5 U/L penicillin and 1 mg/L streptomycin. A total of 4.5×10^5 cells were obtained and each 3×10^4 cell was plated with 1.0 ml culture medium in 35 × 10 mm tissue culture dishes (Falcon, Becton-Dickinson, Primaria, CA) which were placed in an incubator at 37 C under a humidified atmosphere of 5% CO_2 and 95% air. Three days after plating, half of the culture medium was changed to replenish cell nutrients and collected culture medium of all 4.5×10^5 cells served as the hormone assay for GH, LH, FSH, PRL, TSH, and ACTH. Cells were utilized 6 days after plating. All culture cells were washed twice with culture medium without FCS. The medium was then replaced by 1.0 ml DMEM without FCS to avoid the effect of hormones on the cell suspension.

Four plates were cultured in non-FCS medium for 4 h, two with 10^{-6} mol/L TRH and two without TRH. As controls, two plates were cultured in DMEM with 10^{-6} mol/L GHRH. TSH and GH of the collected media were measured.

Effect of increasing doses of T_3 on TRH-induced TSH release in vitro

Tumor cells (1×10^4) were precultured with 10^{-13}, 10^{-11}, 10^{-9}, 10^{-7} mol/L T_3 for 15 h, washed, and then cultured with 10^{-6} mol/L TRH for 4 h. TSH concentration of the media were measured.

Effect of exogenous T_3 on TSH response to TRH 1 yr after surgery

One year after the operation, the T_3 suppression test on TRH-induced TSH response was repeated.

Hormone assay

Concentrations of pituitary hormones as well as those of fT_3 and fT_4 were measured by RIAs. TSH levels in plasma and in the cell culture supernatant were measured by the double antibody RIA of Odell *et al.* (9) using commercial kits (Daiichi RI Laboratory, Tokyo, Japan; normal range, <6 mU/L; sensitivity, 0.5 mU/L). Second IRP 80/558 was used as the standard. The cross-reactivities of LH, FSH, and hCG in this assay were negligible. Glycoprotein α-subunit was determined by a double antibody RIA using reagents obtained from the NIDDK, according the previously reported method (10). The sensitivity of the α-subunit assay was 0.3 μg/L. For the measurement of thyroid hormone autoantibodies, the patient's serum was directly incubated with ^{125}I-T_3 or T_4 analog which did not bind to thyroxine-binding globulin (TBG), followed by bound/free (B/F) separation with polyethyleneglycol, counting the precipitates (5, 6). The molar α-subunit and TSH ratio were calculated on the basis of the following mol wt: TSH, 28,000; and α-subunit, 14,700 (1 ng TSH corresponds to 4.9 μU).

Results

Effect of exogenous T_3 on TSH response to TRH before the operation

Before administration of T_3, TRH caused marked stimulation of TSH secretion. These increases were suppressed by T_3 treatment, though some response was still evident even with 400 mg/day of T_3 (Fig. 2A).

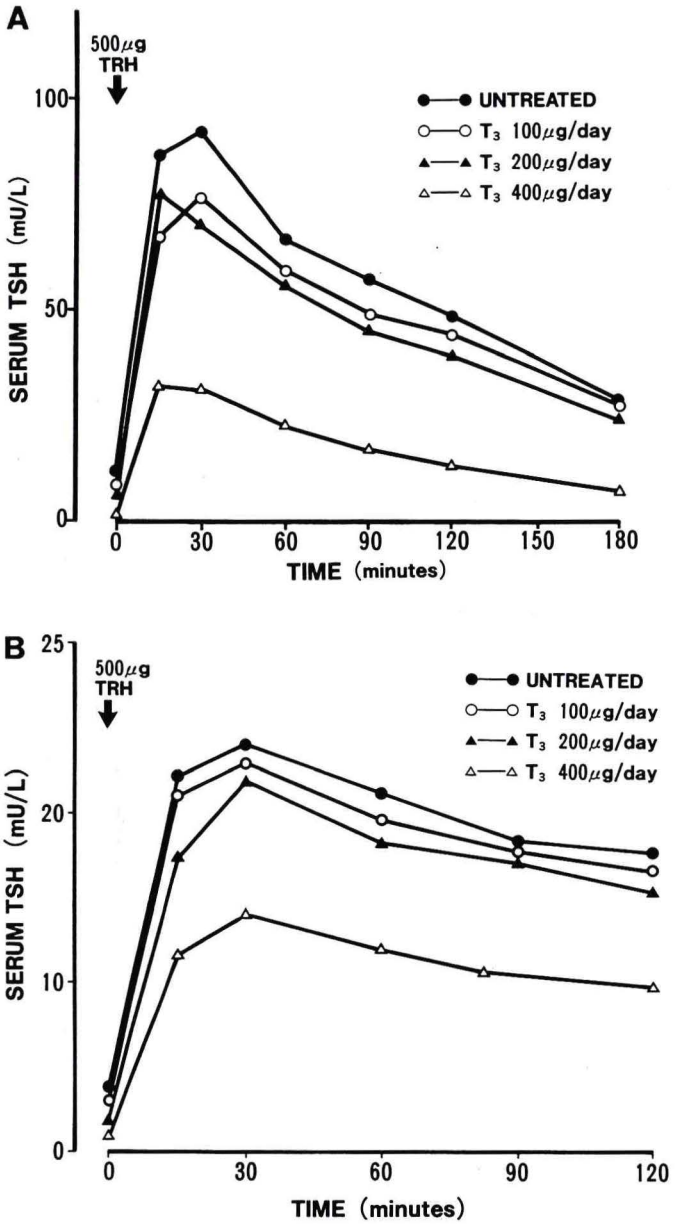

FIG. 2. A, Effect of exogenous T_3 on TSH response to TRH preoperatively. Before the treatment of T_3, TRH caused marked stimulation of TSH secretion. This response was suppressed by exogenous T_3 in a dose-dependent manner, though some response was still evident even with 400 mg/day of T_3. B, Effect of exogenous T_3 on TSH response to TRH postoperatively. Although basal TSH levels remained high, TSH was still responsive to TRH. The peak value, however, was significantly lower than it had been preoperatively.

Histology, immunostaining, and electron microscopy

Tissue fragments of an adenoma with predominantly chromophobic areas were obtained from the surgical specimens. The tumor border was distinct from the nonneoplastic pituitary tissue. No infiltration into normal surrounding tissues was observed. In the adenomatous tissue, there were several islets of variable size, the cells of which were slightly basophilic (Fig. 3A), had abundant cytoplasm and, for the most part, stained positive for both TSH-β (Fig. 3B) and α-subunit and, to a lesser extent, for PRL. Electron micrographs of the cells within the islets characteristically showed small (100–200 nm) secretory granules, frequently lined up along the cell membrane (Fig. 3D). The chromophobe area with occasional TSH-positive cells (Fig. 3C) consisted of sparsely granulated cells with small secretory granules 100–200 nm in diameter, sparse rough endoplasmic reticulum, and moderately developed Golgi complexes (Fig. 3E). The almost complete absence of thyrotrophs in a nontumorous pituitary fragment was also noted, and there were no obvious foci of thyrotroph hyperplasia.

Pituitary hormone secretion and effect of TRH on TSH secretion of tumor cells in vitro

Medium was collected from 4.5×10^5 cells after cultured for 3 days. The concentrations of GH, LH, FSH, PRL, TSH, and ACTH in the collected medium were 3 μg/L, 18 IU/L, 17 IU/L, 9 μg/L, 423 mU/L, and 2 pmol/L, respectively. TSH concentrations in the media of 3×10^4 cells after 4 h incubation without TRH were 12.5 and 12.9 mU/L. On the other hand, TSH concentrations in the media with TRH were 32.9 and 32.9 mU/L. GH concentrations of the media were less than 1 μg/L regardless of presence or absence of added TRH or GHRH.

Effect of increasing doses of T_3 on TRH-induced TSH release in vitro

Increasing the concentration of T_3 suppressed the TSH release stimulated by TRH in a dose-dependent manner as shown *in vivo* (Fig. 4).

Effect of exogenous T_3 on TSH response to TRH 1 yr after surgery

Basal TSH level remained high 1 yr postoperatively, and TSH was still responsive to TRH. The peak value, however, was significantly lower than it had been preoperatively. Exogenous T_3 suppressed the TSH response to TRH, though the suppression was not complete (Fig. 2B).

Discussion

IST may be diagnosed in a patient in whom basal or TRH-stimulated serum concentrations of TSH are inappropriately elevated in the presence of elevated free serum thyroid hormones (2). According to this definition, our patient's diagnosis belongs to this category. The classification of IST depends on whether or not hypersecretion of TSH is associated with a neoplasma (pituitary tumor or nonpituitary ectopic tumor) (3). In general, neoplastic production of TSH appears to be autonomous, that is, unresponsive to either TRH stimulation or T_3 suppression. With regard to the criteria, in the patient described here, TSH was hyperresponsive to TRH and thyroid hormone suppressed both basal and TRH-stimulated TSH. Although hormonal examination strongly suggested that this patient was suffering from non-

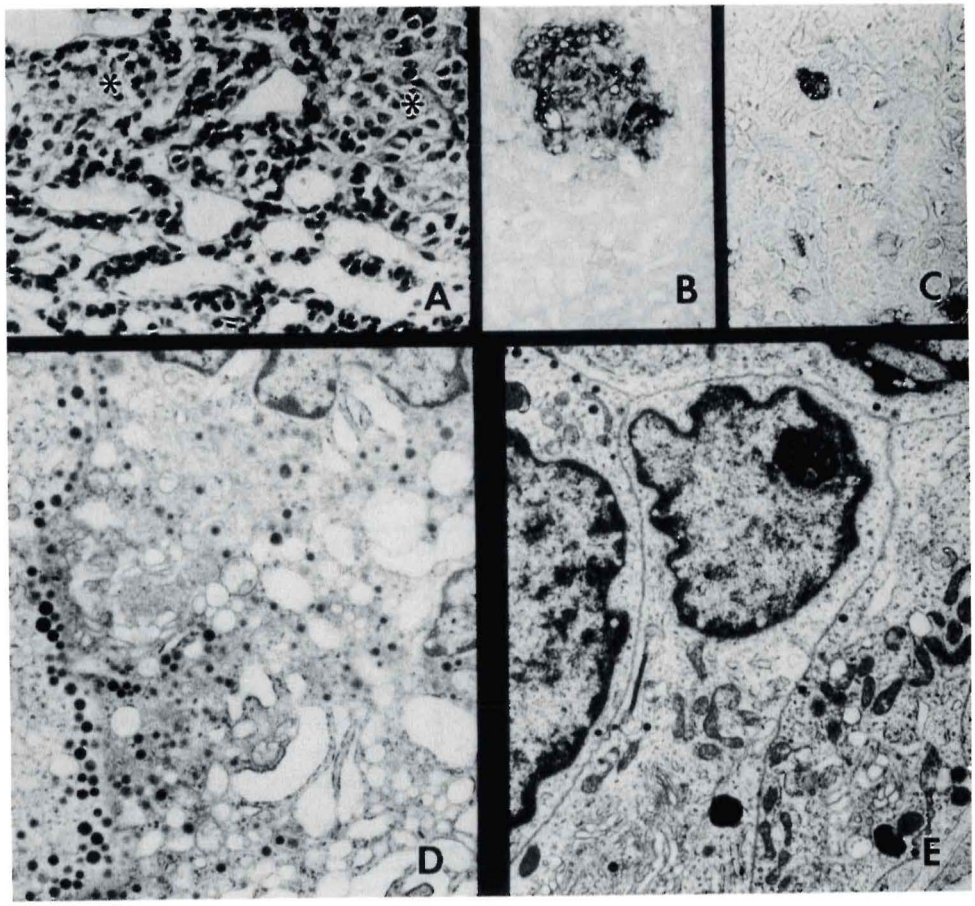

FIG. 3. Histology, immunostaining for TSH, and ultrastructure of the pituitary adenoma. A, Histology demonstrating a chromophobic area with sinusoid-like blood vessels on the *left* and two basophilic islet-like cell clusters (*) (hematoxylin and eosin, ×200). B, Immunostaining of the adenoma for TSH-β. In this tumor area, only one islet-like cell cluster is predominantly positive for TSH-β (immunostain for ABC method, ×100). C, Immunostaining of the adenoma for TSH-β. Single cells or pairs of cells with TSH positivety are scattered within the chromophobic area (immunostain for ABC method, ×100). D, Electron micrograph of the islet-like area consisting of mostly TSH-positive cells. The constituent secretory cells closely resemble well-differentiated thyrotrophs (×13,500). E, Electron micrograph of the chromophobic area. The adenoma cells consist of sparsely granulated cells with small secretory granules 100–200 nm in diameter, sparse rough endoplasmic reticulum, and moderately developed Golgi complexes (×13,500).

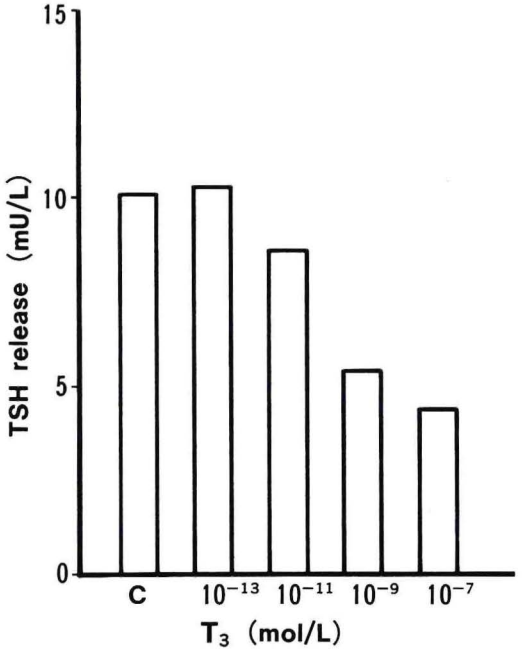

FIG. 4. Effect of increasing doses of T_3 on TRH-induced release of TSH *in vitro*. Tumor cells (1×10^4) were used for this study. Increasing the concentration of T_3 suppressed the TSH release stimulated by TRH in a dose-dependent manner like that *in vivo*.

neoplastic IST, cranial CT and MRI revealed a pituitary adenoma.

Pathological findings of the pituitary adenoma in this patient were unusual and worthy of special consideration. Uniform chromophobe cell proliferation with scattered TSH-β and α-subunit-positive cells are the most common features of TSH-producing tumors. In the present case, however, the adenoma consisted of diffusely proliferating chromophobe cells with scattered spherical islet-like cell foci which were basophilic and mostly positive for TSH-β and α-subunit. The question as to whether this represents heterogeneous differentiation in one tumor or the formation of a new clone, remains to be determined. The islet-like foci which were diffusely positive for TSH might be at a special phase of the secretory cycle of these tumor cells. At any rate, this feature is definitely unusual. Almost complete absence of thyrotrophs in the nontumorous pituitary fragment may be due to suppression by thyroid hormones through a negative feedback mechanism.

Electron micrographs also clearly demonstrated two cell types in chromophobic and chromophilic areas. The former represented less differentiated, sparsely granulated thyrotrophs while the latter were well differentiated and densely granulated.

Previous results of *in vitro* studies of TSH secretion in pituitary adenomas have been variable (11–23). In some reports, adenoma cells were unresponsive to TRH. On the

other hand, some investigators have emphasized that TSH regulation by TRH or thyroid hormone is maintained at nearly normal levels *in vitro* (13–15). In our *in vitro* study, TSH concentration in the culture media was much higher than the other pituitary hormones. Furthermore, TSH secretion was stimulated by TRH and suppressed by T_3 in a dose-dependent manner. This is a very important reflection of hormone activity *in vivo*.

The tumor was selectively removed, including some nonneoplastic area. Neither residual tumor nor recurrence was detected by follow-up CT and MRI. TSH, fT_3, and fT_4, however, were still high, and TSH responded to TRH and was suppressed by T_3 1 yr after surgery. The molar α/TSH ratio decreased from 1.5 (α-subunit, 1.7 μg/L) to 0.7 (α-subunit, 0.4 μg/L). These findings suggested the cryptic existence of nonneoplastic IST (24, 25). This category was divided into two subclasses, generalized and pituitary resistance to thyroid hormone. The case described here had finger tremor, tachycardia, diaphoresis, increased basal metabolic rate, and increased levels of SHBG (26, 27), osteocalcin (28, 29) and angiotensin-converting enzyme (30), which led to the diagnosis of pituitary resistance to thyroid hormone. It is possible that nonneoplastic IST might have existed in this patient, and that hypersecretion of TSH caused by unresponsiveness of the pituitary gland to thyroid hormone led to tumor growth.

TSH-secreting adenoma secondary to hypothyroidism (31, 32), gonadotropin-secreting adenoma secondary to hypogonadism (33, 34), and ACTH-producing adenoma secondary to Addison's disease (35, 36), have been reported. All of these neoplasms are thought to occur due to a lack of hormonal-negative feedback to the pituitary gland. To date, no simultaneous occurrences of pituitary resistance to thyroid hormone and pituitary adenoma have been reported. This is the first report of TSH-producing adenoma associated with pituitary resistance to thyroid hormone, and the unusual histology of this pituitary adenoma will by reevaluated as increased numbers of cases such as this are reported.

Acknowledgment

The authors are grateful for the technical assistance provided by K. Kadoya and Electron Microscopy Laboratory, Kitasato University School of Medicine. The authors wish to thank Dr. K. Kovacs (Department of Pathology, St. Michael's Hospital, University of Toronto) for critical comments on this case. The authors also wish to thank Dr. J. Takamatsu (First Division, Department of Internal Medicine, Osaka Medical College) for measurement of SHBG, osteocalcin, and angiotensin-converting enzyme and for critical comments on this case.

References

1. **Ridgway EC, Weintraub BD, Cevallos JL, Rack MC, Maloof F.** 1973 Suppression of pituitary TSH secretion in the patient with a hyperfunctioning thyroid nodule. J Clin Invest. 52:2783–2792.
2. **Gershengorn MC, Weintraub BD.** 1975 Thyrotropin-induced hyperthyroidism caused by selective pituitary resistance to thyroid hormone: a new syndrome of "inappropriate secretion of TSH." J Clin Invest. 56:633–642.
3. **Weintraub BD, Gershengorn MC, Kourides IA, Fein H.** 1982 Inappropriate secretion of thyroid-stimulating hormone. Ann Intern Med. 95:339–351.
4. **Kourides IA, Ridgway EC, Weintraub BD, Bigos ST, Gershengorn MC, Maloof F.** 1977 Thyrotropin-induced hyperthyroidism: use of alpha and beta subunit levels to identify patients with pituitary tumors. J Clin Endocrinol Metab. 45:534–543.
5. **Rodríguez-Espinosa J, Ordóñez-Llanos J, Gómez-Gerique JA, Mora J.** 1984 Anti-triiodothryonine autoantibodies interfere with two recently commercialized radioimmunoassays for free triiodothyronine. Clin Chem. 30:151–152.
6. **Allan DJ, Murphy F, Needham CA, Barron N, Wilkins TA, Midgley JEM.** 1982 Sensitive test for thyroid hormone autoantibodies in serum. Lancet 2:824.
7. **Hsu SM, Raine L, Fanger H.** 1981 Use of avidin-biotin-peroxidase complex (ABC) in immunoperoxidase techniques: a comparison between ABC and unlabelled antibody (PAP) procedures. J Histochem Cytochem. 29:577–580.
8. **Koide Y, Kugai N, Kimura S, et al.** 1982 A case of pituitary adenoma with possible simultaneous secretion of thyrotropin and follicle-stimulating hormone. J Clin Endocrinol Metab. 54:397–403.
9. **Odell WD, Wilber JF, William EP.** 1965 Radioimmunoassay of thyrotropin in human serum. J Clin Endocrinol Metab. 25:1179–1188.
10. **Kourides IA, Weintraub BD, Levko MA, Maloof F.** 1974 Alpha and beta subunit of human thyrotropin: purification and development of radioimmunoassays. Endocrinology. 94:1411–1421.
11. **Kohler PO, Bridson WE, Rayford PL, Kohler SE.** 1969 Hormone production by human pituitary adenomas in culture. Metabolism. 18:782–788.
12. **Waldhäusel W, Bratusch-Marrain P, Nowotny P, et al.** 1979 Secondary hyperthyroidism due to thyrotropin hypersecretion: study of pituitary tumor morphology and thyrotropin chemistry and release. J Clin Endocrinol Metab. 49:879–887.
13. **Filetti S, Rapoport B, Aron DC, Greenspan FC, Wilson CB, Fraser W.** 1982 TSH and TSH-subunit production by human thyrotropic tumor cells in monolayer culture. Acta Endocrinol (Copenh). 99:224–231.
14. **Mashiter K, Van Noorden S, Fahlbusch R, Fill H, Skrabal K.** 1983 Hyperthyroidism due to a TSH secreting pituitary adenoma: case report, treatment and evidence for adenoma TSH by morphological and cell culture studies. Clin Endocrinol (Oxf). 18:473–483.
15. **Lamberts SWJ, Oosterom R, Verleun T, Krenning EP, Assies H.** 1984 Regulation of hormone release by cultured cells from a thyrotropin-growth hormone-secreting pituitary tumor. Direct inhibiting effects of 3,5,3′-triiodothyronine and dexamethasone on thyrotropin secretion. J Endocrinol Invest. 7:313–317.
16. **Jaquet P, Hassoun J, Delori P, Gunz G, Grisoli F, Weintraub BD.** 1984 Human pituitary adenoma secreting thyrotropin and prolactin: immunohistochemical, biochemical, and cell culture studies. J Clin Endocrinol Metab. 59:817–824.
17. **Spada A, Bassetti M, Martino E, et al.** 1985 *In vitro* studies on TSH secretion and adenylate cyclase activity in human TSH-secreting pituitary adenoma. Effects of somatostatin and dopamine. J Endocrinol Invest. 8:193–198.
18. **Beck-Peccoz P, Piscitelli G, Amr S, et al.** 1986 Endocrine, biochemical, and morphological studies of a pituitary adenoma secreting growth hormone, thyrotropin (TSH) and alpha-subunit: evidence for secretion of TSH with increased bioactivity. J Clin Endocrinol Metab. 62:704–711.
19. **Jameson LJ, Lindell CM, Habener JF.** 1987 Gonadotropin and thyrotropin alpha- and beta-subunit gene expression in normal and neoplastic tissues characterized using specific messenger ribonucleic acid hybridization probes. J Clin Endocrinol Metab. 64:319–327.
20. **Simard M, Mirell CJ, Pekary AE, Drexler J, Kovacs K, Hershman JM.** 1988 Hormonal control of thyrotropin and growth hormone secretion in a human thyrotrope pituitary adenoma studied *in vitro*. Acta Endocrinol (Copenh). 119:283–290.
21. **Kuzuya N, Inoue K, Ishibashi M, et al.** 1990 Endocrine and immunohistochemical studies on thyrotropin (TSH)-secreting pituitary adenomas: responses of TSH, α-subunit, and growth hormone to hypothalamic releasing hormones and their distribution in adenoma cells. J Clin Endocrinol Metab. 71:1103–1111.
22. **Barbarino A, DeMarinis L, Anile C, Maria G.** 1980 Normal pituitary function and reserve after selective transsphenoidal re-

moval of a thyrotropin-producing pituitary adenoma. Metabolism. 29:739–744.
23. **Yovos JG, Falko JM, O'Dorisio TM, Malarkey WB, Cataland S, Capen CC.** 1981 Thyrotoxicosis and a thyrotropin secreting pituitary tumor causing unilateral exophthalmos. J Clin Endocrinol Metab. 53:338–343.
24. **Refetoff S, DeWing LT, DeGroot LJ.** 1969 Familial syndrome combining deaf-mutism, stippled epiphyses, goiter and abnormally high PBI: possible target organ refractoriness to thyroid hormone. J Clin Endocrinol Metab. 27:279–294.
25. **Refetoff S, DeGroot LJ, Benard B, DeWing LT.** 1972 Studies of a sibship with apparent hereditary resistance to the intracellular action of thyroid hormone. Metabolism. 21:723–756.
26. **DeNayer PH, Lambot MP, Desmons MC, Rennotte B, Malvaux P, Beckers C.** 1986 Sex hormone binding protein in hyperthyroxinemic patients: a discriminator for thyroid status in thyroid hormone resistance and familial dysalbuminemic hyperthyroxinemia. J Clin Endocrinol Metab. 62:1309–1312.
27. **Sarne DH, Refetoff S, Rosenfield RL, Farriaux JP.** 1988 Sex hormone-binding globulin in the diagnosis of peripheral tissue resistance to thyroid hormone: the value of changes after short term triiodothyronine administration. J Clin Endocrinol Metab. 66:740–746.
28. **Garrel DR, Delmas PD, Malaval L, Tourniaire J.** 1986 Serum bone Gla protein: a marker of bone turnover in hyperthyroidism. J Clin Endocrinol Metab. 62:1052–1055.
29. **Lukert BP, Higgins JC, Stoskopf MM.** 1986 Serum osteocalcin is increased in patients with hyperthyroidism and decreased in patients receiving glucocorticoids. J Clin Endocrinol Metab. 62:1056–1058.
30. **Yotsumoto H, Imai Y, Kuzuya N, Uchiyama H, Matsuzaki F.** 1982 Increased levels of serum angiotensin-converting enzyme activity in hyperthyroidism. Ann Intern Med. 96:326–328.
31. **Vegenakis AG, Dole K, Braverman LE.** 1976. Pituitary enlargement, pituitary failure, and primary hypothyroidism. Ann Intern Med. 85:195–198.
32. **Samaan NA, Osborne BM, Mackay B, Leavens ME, Ouello TM, Halmi NS.** 1977 Endocrine and morphologic studies of pituitary adenomas secondary to primary hypothyroidism. J Clin Endocrinol Metab. 45:903–911.
33. **Bower BF.** 1968 Pituitary enlargement secondary to untreated primary hypogonadism. Ann Intern Med. 69:107–109.
34. **Kelly LW.** 1963 Ovarian dwarfism with pituitary tumor. J Clin Endocrinol Metab. 23:50–53.
35. **Dexter RM, Orth DN, Abe K, Nicholson WE, Liddle GW.** 1970 Cushing's disease without hypercortisolism. J Clin Endocrinol Metab. 30:573–579.
36. **Dluhy RG, Moore TJ, Williams GH.** 1978 Sella turcica enlargement and primary adrenal insufficiency. Ann Intern Med. 89:513–514.