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Hyperthyroidism Due to a Thyrotropin-Secreting Pituitary Microadenoma

Jeffrey A. Jackson, MD,* Mitchell Smigiel, MD,[†] and John F. Greene, Jr, MD[‡]

A 52-year-old man presented with elevated thyroid hormone levels and an inappropriately normal serum thyrotropin (TSH) (4.0 μ U/mL; normal 0.5 to 6.0 μ U/mL). Computed tomography suggested an intrasellar mass without radiographic sellar enlargement. Serum alpha-subunit was elevated with flat responses of both alpha-subunit and TSH to thyrotropin-releasing hormone. Transsphenoidal adenectomy resulted in clinical and biochemical cure with subsequent development of hypothyroidism with otherwise preserved anterior pituitary function. Pathologic studies demonstrated an 8 mm typical thyrotroph cell adenoma. Early diagnosis of such tumors requires a high index of clinical suspicion and may be facilitated in the future by utilization of highly sensitive TSH assays. (Henry Ford Hosp Med J 1987;35:198-200)

Thyrotropin (TSH)-secreting pituitary adenomas are a rare cause of goitrous hyperthyroidism (1,2). These cases have often been recognized after thyroid ablative therapy has already been given when either paradoxical elevation of TSH levels or extrasellar manifestations are discovered. Most of these patients have had initial basal TSH levels above the upper limit of normal with tumors of considerable size at diagnosis. This report describes the clinical and hormonal features of a hyperthyroid patient who presented with inappropriately normal serum TSH and was found to have a thyrotroph cell pituitary microadenoma.

Case Report

A 52-year-old man was self-referred for a second opinion regarding recently abnormal thyroid function tests. For six weeks he had had subjective fatigue without heat intolerance, weight loss, palpitations, or headache. He was mildly tachycardic with a small goiter (≤ 25 g) and minimal fine tremor of outstretched hands. No ophthalmopathy or dermopathy was present. His testes were somewhat small (2.5 x 3.5 cm). Serum thyroxine (T_4) was 20.4 μ g/dL (normal 5.5 to 11.5 μ g/dL), with triiodothyronine (T_3) resin uptake 46% (normal 35% to 45%) and free T_4 index 9.3 (normal 2.0 to 5.2). Serum T_3 was 248 ng/dL (normal 100 to 200 ng/dL). Basal serum TSH was 3.8 to 4.0 μ U/mL (normal 0.5 to 6.0 μ U/mL). Twenty-four hour 131 I thyroidal uptake was 54.1% (normal 10% to 30%). No enlargement or erosion was detected by sellar tomography. High-resolution pituitary computed tomography (CT) suggested an intrasellar mass without suprasellar extension (Fig 1). Visual field perimetry was normal.

Further endocrine testing included normal serum testosterone (0.71 μ g/dL; normal 0.3 to 1.0 μ g/dL), prolactin, growth hormone, and cortisol. Basal alpha-subunit level was 9.8 ng/mL (normal < 3 ng/mL) with an alpha-subunit to TSH molar ratio of > 15.0. Serum gonadotropins were mildly elevated (Table). Glycoprotein hormone responses to thyrotropin-releasing hormone (TRH) and luteinizing hormone-releasing hormone (LHRH) testing are shown in the Table.

Methimazole therapy (30 mg daily) was given for two months preoperatively and lowered the free T_4 index to 5.2, although serum TSH increased to 25.3 μ U/mL without change in alpha-subunit level (9.4 ng/mL). At transsphenoidal surgery a microadenoma (8 mm)

was found, which required subtotal hypophysectomy for adequate resection.

Pathologic study of the tumor demonstrated a typical thyrotroph cell adenoma. Diffuse immunostaining for alpha-subunit and TSH (Fig 2) was present with negative or nonspecific cellular immunoreactivity for prolactin, ACTH, luteinizing hormone, and follicle-stimulating hormone (FSH). A few scattered cells exhibited immunopositivity for growth hormone. Ultrastructural features included long cytoplasmic processes, well-developed Golgi complexes, and secretory granules generally 100 to 300 nm in size.

Postoperative recovery was routine; on the fourth postoperative day free T_4 had fallen to 2.8 with undetectable serum TSH. One month later, the alpha-subunit level was 0.8 ng/mL. Gonadotropin levels were unchanged. The patient developed hypothyroid symptoms six weeks postoperatively and has been maintained on l- T_4 replacement and intermittent intranasal desmopressin with otherwise intact anterior pituitary function and no subsequent tumor recurrence.

Discussion

A high index of clinical suspicion led to subsequent studies in this patient which unequivocally demonstrated the presence of a TSH-secreting pituitary microadenoma. Determination of basal serum TSH using a sensitive assay technique in diffuse goitrous hyperthyroidism and no other stigmata (ophthalmopathy and dermopathy) of Graves' disease is the best method to identify patients with inappropriate TSH secretion (1). With sensitivity of our TSH assay (Immunoradiometric technique, Vitek Systems, Hazelwood, MO), hyperthyroid values are generally < 0.5 μ U/mL. Approximately 25% of patients with thyrotroph

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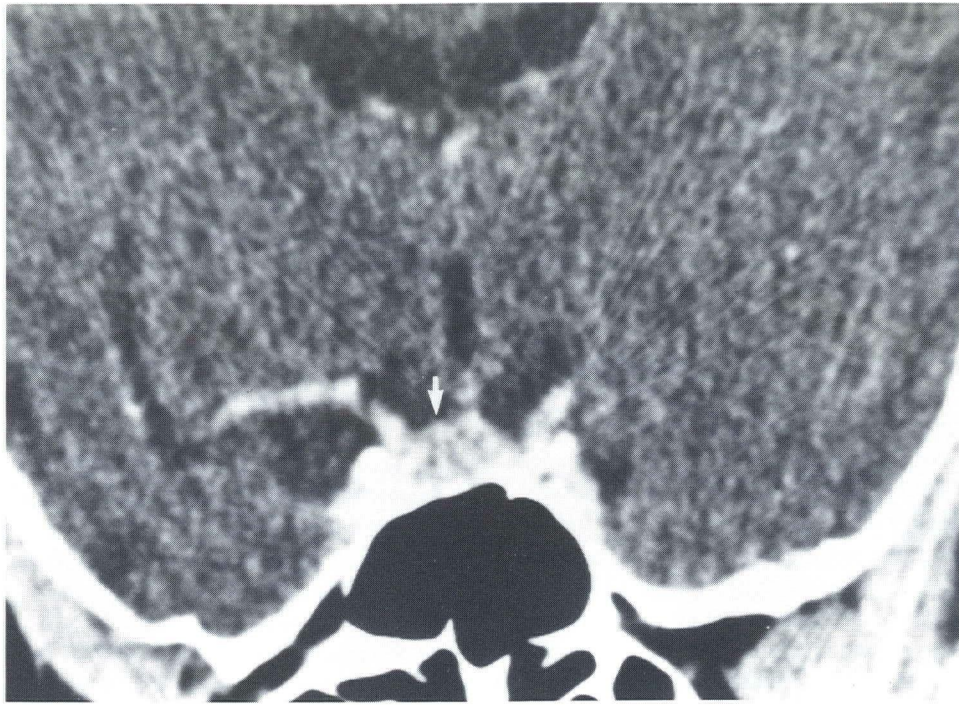


Fig 1—High-resolution contrast-enhanced direct coronal computed tomography scan showing abnormal convexity of the upper border of the pituitary gland (arrow).

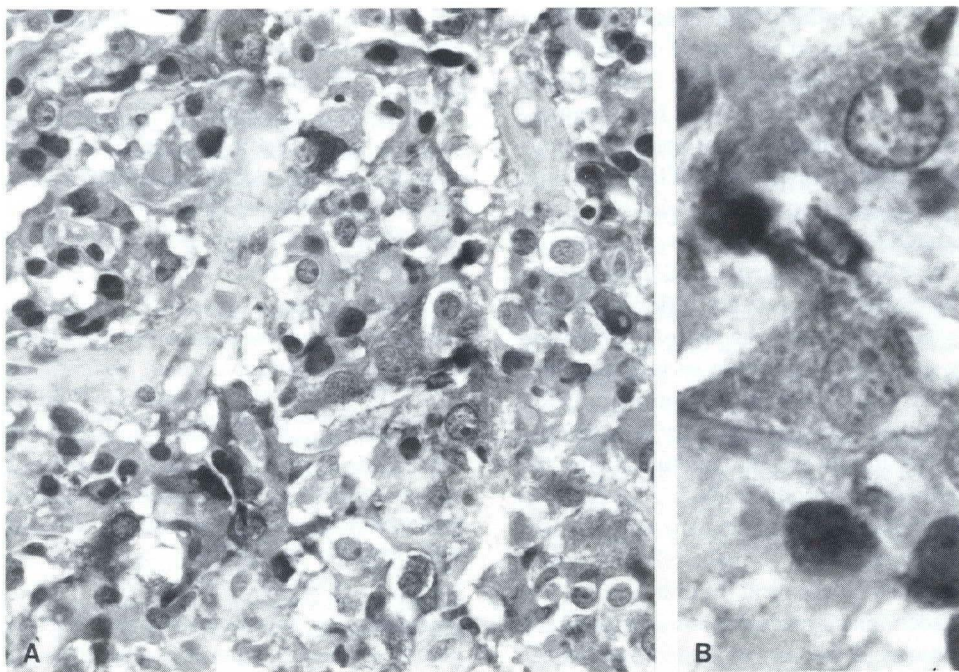


Fig 2—Diffuse cytoplasmic immunoreactivity of tumor cells for TSH. (A) Immunoperoxidase (X400). (B) Immunoperoxidase (X1400). (Vector Laboratories, Inc, Burlingame, CA; rabbit antihuman TSH antiserum, 1:1000, counterstained with hematoxylin.)

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Table
Results of Dynamic Testing

	TRH* TEST (500 µg)		LHRH* TEST (100 µg)		LH*	FSH*
	Thyrotropin (µU/mL)	alpha-Subunit (ng/mL)	Thyrotropin (µU/mL)	alpha-Subunit (ng/mL)		
Baseline	7.4	9.7	5.4	6.7	45	28
20 minutes	7.0	9.5	—	—	—	—
30 minutes	6.9	9.2	5.0	10.5	128	48
60 minutes	—	—	4.9	9.5	99	45

*TRH = thyrotropin-releasing hormone, LHRH = luteinizing hormone-releasing hormone, LH = luteinizing hormone, and FSH = follicle-stimulating hormone.

cell adenomas have had TSH values within the normal range as in this case (2).

Since the first description of a pituitary tumor associated with hyperthyroidism (3), over 50 patients with TSH-secreting adenomas have been reported (1,2,4-6). To our knowledge only three hyperthyroid patients with TSH-secreting pituitary microadenomas have been described previously (7-9); two of these patients were cured after transsphenoidal surgery alone (7,8), and one patient developed transient biochemical hypothyroidism three months after selective microadenectomy (7). Conceivably, our patient may in time regain normal thyrotroph cell function, analogous to the temporary hypoadrenalism that develops after successful adenectomy in Cushing's disease (10).

Preoperative preparation of our patient was satisfactorily accomplished by antithyroid therapy alone. This resulted in a six-fold increase in serum TSH similar to that observed in 50% of other thyrotroph cell adenoma cases (5,6,8). Recent use of a long-acting somatostatin analog preoperatively in such patients was shown to be rapidly effective in lowering thyroid hormone levels (11) and may become the preparative approach of choice.

Our patient did not exhibit TSH responsiveness to dynamic testing with TRH or LHRH. Similarly, flat TSH response to TRH has been demonstrated in most but not all patients with TSH-secreting pituitary adenomas (1,2,4,5,8). Lack of TSH (12) and alpha-subunit (13) responses to LHRH have been reported previously. Autonomy of alpha-subunit secretion in our patient was supported by lack of response to TRH and antithyroid drug therapy. The slight response of alpha-subunit to LHRH may have originated from nonneoplastic gonadotroph cells. Gonadotropins were hyperresponsive to LHRH and remained unchanged postoperatively, probably reflecting subtle testicular hypofunction despite normal total testosterone levels; the tumor did not show specific gonadotropin immunostaining. In one other report of a thyrotroph cell adenoma with serum FSH elevation (12), the possibility of cross-reactivity between the FSH antiserum and alpha-subunit was not excluded, and tumoral FSH immunostaining was unconvincing.

Preoperative diagnosis of TSH-secreting pituitary adenomas requires demonstration of inappropriately normal or elevated serum TSH at the time of clinical and biochemical hyperthyroidism and visualization of a microadenoma or macroadenoma by pituitary imaging (CT or nuclear magnetic resonance). Supportive data include lack of TSH response to TRH testing and elevation of the alpha-subunit to TSH molar ratio (> 1.0) (14). Pathologic confirmation includes typical immunohistochemical TSH staining and ultrastructural features of thyrotropic adenomas (9). Expanded utilization of highly sensitive TSH assays may promote early diagnosis of

such tumors prior to gross sellar enlargement, thus facilitating primary surgical cure as was demonstrated in this patient.

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