Endocrine, *vol. 25, no. 2, 141–145, November 2004* 0969–711X/04/25:141–145/$25.00

A Rare Case and a Rapid Tumor Response to Therapy

Dramatic Reduction in Tumor Size During Octreotide Treatment in a Patient with TSH-Secreting Pituitary Macroadenoma

Cihangir Erem,[1] Arif Hacihasanoglu,[1] Ahmet Sari,[2] Halil Önder Ersöz,[1] Kubilay Ukinç,[1] and Sami Fidan[1]

[1]*Department of Internal Medicine, Division of Endocrinology and Metabolism; and* [2]*Department of Radiology, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey*

Thyrotropin (TSH)-secreting pituitary adenomas are the less frequent form of presentation of pituitary tumors. The presence of somatostatin receptors on TSH-secreting adenomas allows treatment of central hyperthyroidism with somatostatin analogs. We report a 21-yr-old woman with TSH-secreting pituitary macroadenoma, who was diagnosed based on the symptoms of hyperthyroidism, the lack of inhibition of serum TSH despite an increased serum free thyroxine (FT_4), a low response of serum TSH to thyrotropin-releasing hormone, and a pituitary tumor as revealed by magnetic resonance imaging. The treatment with the somatostatin analog octreotid resulted in inhibition of serum TSH and FT_4 to euthyroid levels with concomitant clinical improvements such as the disappearance of sweating, tachycardia, and finger tremors within 7 d. The tumor size diminished dramatically within 6 wk during treatment of one monthly im injection of 20 mg octreotide-LAR. These effects were continued over 2 yr after the start of octreotide-LAR therapy. Therefore, octreotide-LAR appears to be a useful therapeutic tool to facilitate the medical treatment of TSH-secreting pituitary tumors.

Key Words: TSH-secreting pituitary adenoma; octreotide; tumor shrinkage.

Introduction

TSH-secreting pituitary adenomas are rare, but are now recognized with increased frequency due to the development of more sensitive and specific TSH assays *(1)*. Generally they present as macroadenomas with symptoms related to mass effect and hyperthyroidism. Surgical resection can be curative for microadenomas, whereas incomplete resection is common large tumors *(2)*.

Received September 21, 2004; Revised October 17, 2004; Accepted November 2, 2004.

Author to whom all correspondence and reprint requests should be addressed: Prof. Dr. Cihangir Erem, K.T.Ü. Tip Fakültesi, Hastaliklari Anabilim Dali, 61080, Trabzon/Turkey. E-mail: cihangirerem@hotmail.com

The presence of somatostatin receptors on TSH-secreting pituitary adenomas has allowed consideration of treatment with somatostatin in patients with TSH-dependent hyperthyroidism related to TSH-secreting pituitary tumors *(3–5)*. Somatostatin is an endogenous hypothalamic peptide with a short half-life that inhibits TSH secretion either in physiological conditions *(6)* or in patients with TSH-secreting pituitary adenomas *(7)*. Octreotide, a synthetic somatostatin analog with a half-life of between 80–110 min, is administered sc two or three times daily or continuously using portable pumps. Octreotide treatment suppresses TSH secretion in more than 90% of TSH-secreting pituitary adenomas, normalizes thyroid hormone concentrations in about 70% of the patients, and decreases adenoma size in about 50% of all cases *(8–10)*. To avoid drawbacks such as multiple daily injections or the use of portable pumps, a long-acting release form of the somatostatin analog octreotide has been produced. It consists of octreotide acetate encapsulated with a biodegradable polymer (octreotide-LAR), and this depot formulation is injected im every 4 wk. We report that a rare case with TSH-secreting pituitary macroadenoma showing dramatic reduction in size during octreotide-LAR treatment.

Case Report

A 21-yr-old female was admitted to the division of Endocrinology and Metabolism with a 1-yr history of severe headache, palpitation, nervousness, sweating, heat intolerance, finger fine tremor and 6 kg weight loss. She had been mistakenly diagnosed and treated as Graves' disease for 9 mo. Blood pressure was 140/80 mmHg and sinus tachycardia (120/min) was found. She had enlarged thyroid gland (grade 2 diffuse goiter). Routine laboratory tests and chest X-ray were normal. Antithyroglobulin, antithyroidperoxidase, and TSH receptor antibodies were within the normal ranges. Plasma TSH levels were within the reference range (2.62 mIU/L, normal range 0.27–4.2), but were not suppressed. Serum total triodothyronine (TT_3) was 2.20 ng/mL (normal range 0.8–2.0), serum total thyroxine (TT_4) was 17.45 µg/dL (normal range 5.1–14.1), serum free-triodothyronine (FT_3) was 5.40 pg/mL (normal range 1.8–4.6), and free

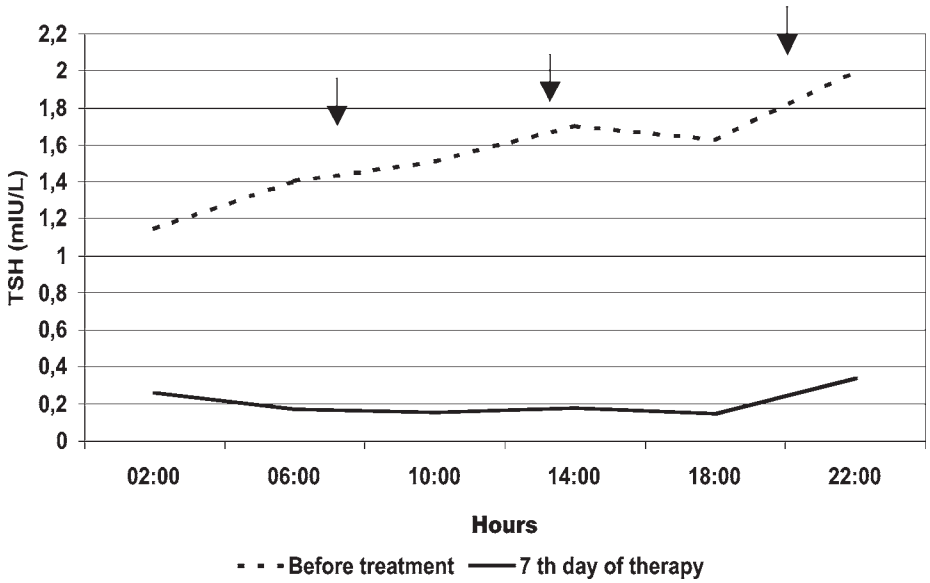

Fig. 1. The levels of plasma TSH over 24 h on the baseline (before treatment) and the 7th day of treatment with octreotide (sc injection, 3 × 100 μg/d). Arrows indicate the time of subcutaneous injections of octreotide.

thyroxine (FT_4) was 3.01 ng/dL (normal range 0.9–1.7). In diurnal rhythm, basal concentrations of TSH varied from 1.15 to 2.0 mIU/L (hour 6.00: 1.41, 10.00: 1.52, 14.00: 1.71, 18.00: 1.63, 22.00: 2.0, and 2.00: 1.15 mIU/L) (Fig. 1). Serum α-subunit of glycoprotein hormones was not measured. No other pituitary-dependent endocrine abnormalities was found; FSH, LH, estradiol, GH, ACTH, prolactin, and cortisol were within the normal ranges. TRH stimulation showed blunt response of TSH (TSH levels, baseline 1.94, 30 min 2.59, 60 min 2.15 and 90 min 2.10 mIU/L, respectively). The sex hormone-binding globulin level was also slightly high (116 nmol/L, normal range 18–114 nmol/L). The patient had no impaired visual field.

The pituitary MRI showed a macroadenoma measuring 2 cm in diameter (Fig. 2). Thyroid ultrasonography confirmed the presence of an enlarged gland. Clinically, pituitary adenoma secreting TSH was diagnosed. Antithyroid drugs were not administered.

Octreotide administered at a dose of 50 mg sc three times a day was started and the dose was increased to 100 mg sc three times after 3 d. After 14 d, the patient received one monthly im injection of 20 mg octreotide-LAR. TSH were measured every 4 h during the 7th day of sc octreotide therapy (hours 6.00: 0.17, 10.00: 0.16, 14.00: 0.18, 18.00: 0.15, 22.00: 0.34 and 2.00: 0.26 mIU/L) (Fig. 1). The normalization of serum peripheral thyroid hormones was achieved after 7 d sc octreotide of treatment (TT_3: 0.96 ng/mL; TT_4: 11.42 μg/dL; FT_3: 2.12 pg/mL; and FT_4: 1.69 ng/dL). After 6 wk, 6.5, 13.5, and 23 mo of octreotide-LAR treatment, MRI examinations were performed. MRI revealed a dramatic reduction in tumor size (Fig. 3). On T1-weighted MR, the tumor mass was observed as a crescent-shaped nonenhancing hypointense area.

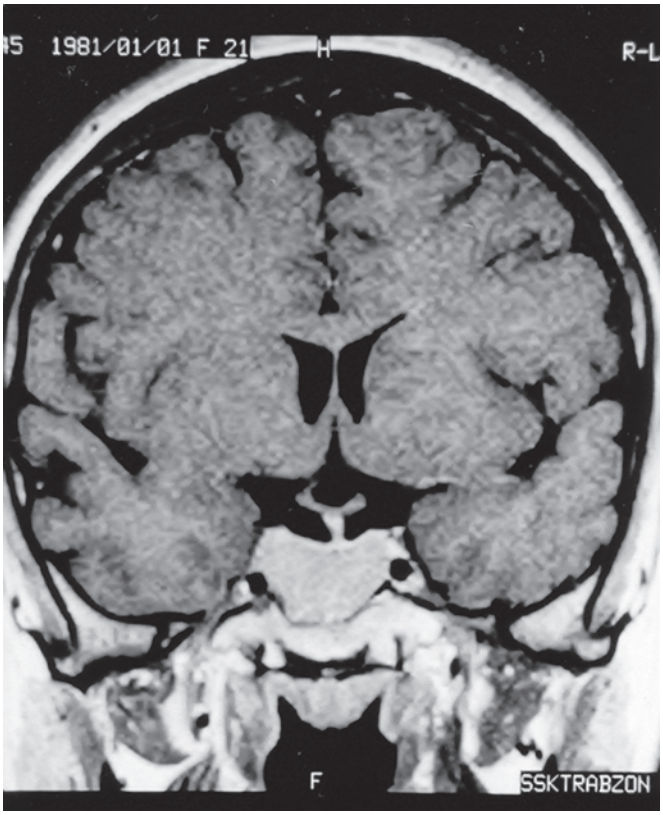

Fig. 2. Contrast enhanced T1-weighted coronal MRI scan of TSH-secreting pituitary adenoma before treatment with octreotide-LAR. MRI shows a macroadenoma of the pituitary gland before treatment.

Discussion

TSH-secreting pituitary adenomas are rare, representing less than 1% of all pituitary tumors *(1,11)* and cause secon-

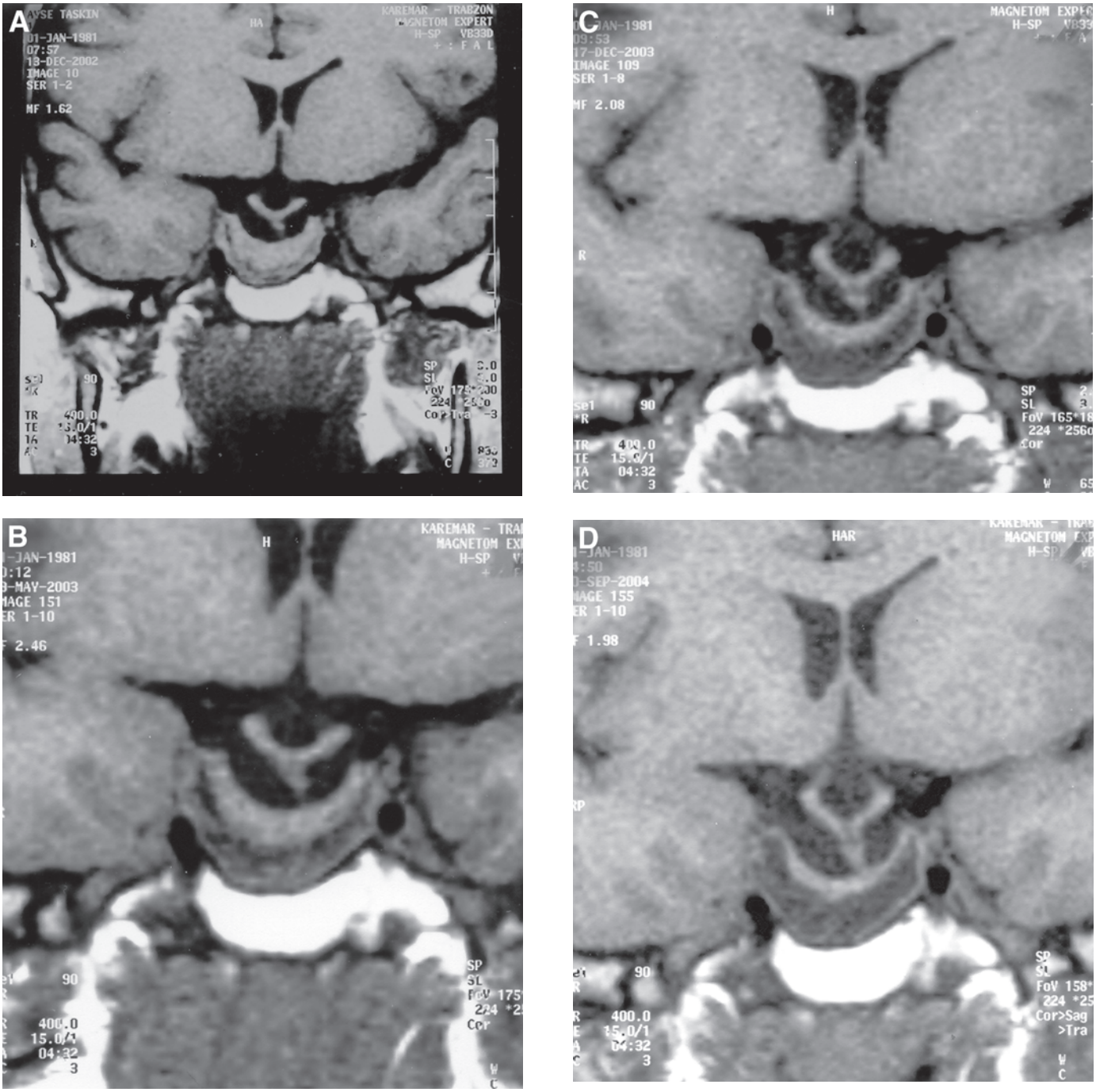

Fig. 3. Nonenhanced T1-weighted coronal MR images obtained at the level of pituitary stalk. MR scan shows that octreotide-LAR treatment for 6 wk resulted in a marked tumor size reduction (**A**). Crescent-shaped hypointense area which consisted of necrosis; 6.5 mo after treatment (**B**), 13.5 mo after treatment (**C**), and approx 2 yr after treatment (**D**). MR image shows progressive increase in the necrotic area.

dary or central hyperthyroidism. The prevalence in general population is one to two cases per million with the introduction of ultrasensitive TSH assays, the frequency of diagnosis seems to increase. Indeed, the number of reported cases of TSH-secreting pituitary adenomas has tripled since the late 1980s *(12)*. A report confirms this trend in a large surgical series, indicating that the occurrence of TSH-secreting pituitary adenomas increased from less than 1% to 2.8% from 1989 to 1991 *(13)*. TSH is a glycoprotein composed of an α-subunit, which is identical with that of LH and FSH, and a β-subunit, which is unique and confers specificity. Most TSH-secreting pituitary adenomas secrete an excess of α-subunit and often the only indicator of a pituitary adenoma is an abnormal ratio of α-subunit/intact TSH *(1,12)*. Despite recent oncogenic studies, the etiology of these tumors, known to be monoclonal in nature, is still unknown *(11)*.

The differential diagnosis of elevated TSH in the face of elevated FT_4 and FT_3 would be a resistance to thyroid hormone (RTH). In unclear cases, the measurement of the serum α-subunit level can be helpful, which was, however, not necessary in the present case. A blunted TSH response to TRH and the absence of TSH suppression by T_3 were suggestive of a tumor *(1)*. TSH response to TRH, however, cannot exclude the presence of an adenoma *(14)*. Laboratory studies and dynamic tests alone may not provide results discriminating between tumorous and nontumorous TSH hypersecretion. Careful examination of the pituitary by MRI or CT scan is indicated in all patients with inappropriate secretion of TSH *(14)*. MRI lesions are almost exclusively found in TSH-secreting pituitary adenomas [98% to according to Beck-Peccoz et al. *(1)*] and very rarely in RTH [2% according to *(1)*].

The optimal treatment of TSH-secreting pituitary adenoma is as yet undetermined. About two-thirds of TSH-secreting pituitary adenomas are under control with pituitary surgery and/or irradiation *(1)*. The remaining patients require alternative pharmalogical therapy. Pituitary tumor cells express somatostatin receptor on their surface. Octreotide suppresess TSH secretion via a G protein–mediated inhibition of adenylcyclase and also has antiproliferative effects by inhibiting mitogenic signaling and by inducing apoptosis *(15)*.

In the light of this knowledge, octreotide treatment of TSH-secreting pituitary adenomas has been used in the last few years *(10,16,17)*. Octreotide is a valuable medical treatment option for TSH-secreting pituitary adenomas *(4)*. Our case illustrates the therapeutic potential of this drug. TSH was suppressed and thyroid hormone levels returned to normal levels within 7 d. Our observation of a rapid fall is in agreement with that of Chayen et al. *(18)* and Fischler et al. *(16)*, who described a substantial fall in TSH within hours and a normalization of T_3 and T_4 within 4 d. In these cases, the administration of antithyroid drugs was not necessary *(8)*. In the literature, normalization of TSH levels has been found in 88–92% of the patients treated with octreotide, and a normalization of the thyroid hormone levels in 72–95% *(1,19,20)*.

Another interesting and striking feature of our case is the substantial reduction of the tumor size during a 6-wk treatment of octreotide, but, initially, few reports were published *(13,21,22)*; 52% patients receiving long-term therapy with octreotide had a clear shrinkage of the tumor mass *(1,19)*. Socin et al. reported that only 5 out of 13 cases demonstrated a significant tumoral shrinkage with somatostatin analogs when used as primary treatment *(20)*. In our case, the reduction in tumor size was dramatic as similar to that seen in patients with prolactinoma who received bromocriptine therapy. The mechanism through which octreotide induces a shrinkage has not yet been established. Although no striking morphological changes in GH-secreting adenomas are associated with octreotide treatment *(23)*, cell shrinkage secondary to reduced cytoplasmic volume might occur *(24)*. There is no evidence of a direct tumoricidal effect of octreotide. Recent studies have shown that octreotide inhibits cell proliferation through stimulation of tyrosine phosphatase and inositol phospholipid/calcium pathway *(25)*. In addition to these mechanisms, in our case an another cause of reduction of the tumor may be necrosis of tumor.

Primary treatment with somatostatin analogs may be a reasonable option in patients wih TSH-secreting pituitary macroadenomas or invasive tumors that are at high risk of not being cured by surgery. Therefore, long-term octreotide treatment may be alternative therapy method vs surgical therapy. However a definitive conclusion requires a randomized study in which more patients with TSH-secreting pituitary tumors are treated with long-acting release somatostatin analogs vs surgery and/or radiotherapy *(3,20)*.

Mild to moderate side effects are noted by one-third of patients, including pain at the injection site, abdominal pain, diarrhea and steatorrhea, vitamin B_{12} malabsorption, and gastritis. We observed cholelithiasis 12 mo after octreotide-LAR treatment in our patient. Cholecystectomy was performed. We showed that octreotide-LAR is effective in controlling hyperthyroidism, but several practical problems should be solved before established octreotide-LAR as the therapeutic method for the control of TSH-secreting adenoma. The benefits of treatment must be weighed against the risk of adverse effects associated with the long-term treatment. The high cost of treatment should also be considered.

Transsphenoidal tumor resection remains the treatment of choice *(26–29)*. We had also previously considered transsphenoidal surgery for patient. The operation was to have been performed after ensuring euthyroidism and reduction of the tumor size by octreotide-LAR therapy. Because of the dramatic reduction in tumor size, we did not plan surgical treatment. In conclusion, our case shows the efficacy and safety of octreotide-LAR in TSH-secreting pituitary adenoma. Octreotide-LAR appears to be a useful therapeutic tool to facilitate the medical treatment of TSH-secreting pituitary tumors.

References

1. Beck-Peccoz, P., Brucker-Davis, F., Persani, L., Smallridge, R. C., and Weintraub, B. D. (1996). *Endocr. Rev*. **17,** 610–638.
2. McCutcheon, I. E., Weintraub, B. D., and Oldfield, E. H. (1990). *J. Neurosurg.* **73,** 674–683.
3. Caron, P., Arlot, S., Bauters, C., et al. (2001). *J. Clin. Endocrinol. Metab.* **86,** 2849–2853.
4. Bertherat, J., Brue, T., Enjalbert, A., et al. (1992). *J. Clin. Endocrinol. Metab.* **75,** 540–546.
5. Losa, M., Magnani, P., Mortini, P., et al. (1997). *Eur. J. Nucl. Med.* **24,** 728–731.
6. Siler, T. M., Yen, S. S. C., Vale, W., and Guillemin, R. (1974). *J. Clin. Endocrinol. Metab.* **38,** 742–745.
7. Reschini, E., Guistina, G., Cantalemessa, L., and Perrachi, M. (1976). *J. Clin. Endocrinol. Metab.* **46,** 924–927.

8. Chanson, P. H., Weintraub, B. D., and Harris, A. G. (1993). *Ann. Intern. Med.* **119,** 236–240.
9. Chanson, P. and Warnet, A. (1992). *Metabolism* **4,** 62–65.
10. Comi, R. J., Gesundheit, N., Murray, L., Gorden, P., and Weintraub, B. D. (1987). *N. Engl. J. Med.* **317,** 12–17.
11. Scoric, T., Korsic, M., Zarkovic, K., et al. (1999). *Eur. J. Endocrinol.* **140,** 528–537.
12. Beck-Peccoz, P. and Persani, L. (2001). In: *TSH-producing adenomas*. DeGroot, L. J. and Jameson, J. L. (eds). W.B. Saunders Company, Philadelphia, pp. 321–328.
13. Minderman, T. and Wilson, C. B. (1993). *J. Neurosurg.* **79,** 521–527.
14. Shimatsu, A., Murabe, H., Kamoi, K., Suzuki, Y., and Nakao, K. (1999). *Endocr. J.* **46,** 113–123.
15. Srikant, C. B. (1995). *Biochem. Biophys. Res. Commun.* **209,** 400–406.
16. Fischler, M. P. and Reinhart, W. H. (1999). *J. Endocrinol. Invest.* **22,** 64–65.
17. Beck-Peccoz, P., Moriotti, S., Guillausseau, P. J., et al. (1989). *J. Clin. Endocrinol. Metab.* **68,** 208–214.
18. Chayen, S. D., Gross, D., Makhoul, O., and Glaser, B. (1992). *Horm. Metab. Res.* **24,** 34–38.
19. Beck-Peccoz, P. and Persani, L. (2002). *Pituitary* **5,** 83–88.
20. Socin, H. V., Chanson, P., Delemer, B., et al. (2003). *Eur. J. Endocrinol.* **148,** 433–442.
21. Warnet, A., Lajeunie, E., Gelbert, F., et al. (1991). *Acta Endocrinol. (Copenh.)* **124,** 487–491.
22. Lee, E. J., Kim, K. R., Lim, S. K., et al. (1994). *Eur. J. Endocrinol.* **131,** 109–112.
23. Ezzat, S., Horvath, E., Harris, A. G., and Kovacs, K. (1994). *J. Clin. Endocrinol. Metab.* **79,** 113–118.
24. George, S. R., Kovacs, K., Asa, S. L., Horvath, E., Cross, E. G., and Burrow, G. N. (1987). *Clin. Endocrinol.* **26,** 395–405.
25. Buscail, L., Eseve, J. P., Saint-Laurent, N., et al. (1995). *Proc. Natl. Acad. Sci.USA* **92,** 1580–1584.
26. Losa, M., Giovanelli, M., Persani, L., Mortini, P., Faglia, G., and Beck-Peccoz, P. (1996). *J. Clin. Endocrinol. Metab.* **81,** 3084–3090.
27. Hubalewska-Hola, A., Fross, K., Kostecka-Matyja, M., et al. (2003). *Przegl. Lek.* **60,** 768–771.
28. Buchfelder, M. (2002). *The Endocrinologist* **12,** 117–125.
29. Smallridge, R. C. (2001). *Curr. Opin. Endocrinol. Diabetes* **8,** 253–258.