

Recombinant Human Thyrotropin for Management of Metastatic Differentiated Thyroid Carcinoma in Patients With Deficient Reserve of Endogenous Thyrotropin

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Radioiodine (RAI) therapy for metastatic follicular cell-derived thyroid cancer (FCDC) requires elevated levels of serum TSH, usually achieved by withdrawal of thyroxine therapy. This is not possible in FCDC associated with hypopituitarism, because of the absence of endogenous TSH. However, the advent of recombinant human TSH (rhTSH) has made diagnostic ¹³¹I whole body scans and subsequent RAI therapy possible for patients with FCDC who have deficiency of endogenous TSH. Recently, several reports have been published of patients with metastatic FCDC and pituitary tumor treated after rhTSH administration. We describe 2 cases of FCDC with hypopituitarism, in which therapeutic RAI intervention was possible only with rhTSH administration.

Materials and Methods: We searched our medical records from 1950 through 1999 to determine the prevalence of FCDC metastases to the pituitary.

Results: We identified 19 cases of FCDC with concomitant hypopituitarism but only 1 with metastasis of FCDC to the sellar region. Of the

19 patients, 2 were treated with rhTSH before RAI therapy.

Conclusions: Although metastasis of FCDC to the pituitary is rare as shown by our study, association of pituitary insufficiency with FCDC is more common. The availability of rhTSH has improved therapy for these patients.

Key Words: Hypopituitarism; Radioisotope therapy; Thyroid cancer; Thyrotropin

Introduction

Radioiodine (RAI) therapy for metastatic follicular cell-derived thyroid cancer (FCDC) requires an elevated concentration of serum TSH, which is usually achieved by stopping therapy with thyroxine. However, a major drawback of discontinuing therapy is the development of symptomatic hypothyroidism with its associated morbidity. Another concern is the potential effect that prolonged elevation of concentrations of TSH have on accelerated tumor growth. Absence of endogenous TSH due to concomitant pituitary disease also prevents effective RAI treatment for patients with differentiated thy-

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roid carcinoma after discontinuing therapy with thyroxine.

With the advent of recombinant human TSH (rhTSH), diagnostic RAI whole body scans (WBS) and subsequent effective therapy for these patients have been possible. Recently, several reports have been published of patients with metastatic FCDC who had inadequate concentrations of endogenous TSH and who were treated after rhTSH stimulation.¹⁻⁴ The causes of hypopituitarism in these cases have included empty sella syndrome,⁴ metastatic papillary thyroid cancer (PTC),^{2,3} and prior pituitary surgery for Cushing disease.¹ To this growing list, we add 2 cases of FCDC with concomitant pituitary abnormalities, one due to metastasis and the other to a null-cell pituitary adenoma. Both were treated with RAI after rhTSH stimulation when discontinuation of thyroxine therapy failed to elicit an endogenous TSH response. We also report on the frequency of association of pituitary failure and sellar metastasis with FCDC.

Methods

After receiving approval from the Mayo Foundation Institutional Review Board for a retrospective analysis of medical records, we searched the Mayo Clinic archives for patients evaluated from 1950 through 1999 who had both FCDC and hypopituitarism. We also scanned our FCDC database to determine the total number of patients with FCDC from 1950 through 1999 who had primary surgery at our institution.

Results

From 1950 through 1999, a total of 2,286 patients with PTC, 130 with follicular thyroid carcinoma (FTC), and 129 with Hürthle cell carcinoma had primary surgery at our institution, for a total of 2,545 patients with FCDC. Among these 2,545 cases, we found only 19 (0.75%) in which hypopituitarism was associated with the diagnosis of FCDC. Among the 19 cases, hypopituitarism was due to pi-

tuitary adenoma in 10 patients (53%), to suprasellar chordoma in 1 (5%), and to subarachnoid hemorrhage in 1 (5%); 6 (32%) were idiopathic. In only 1 patient (0.04%), our patient 1, was hypopituitarism due to pituitary metastasis of FCDC.

Case Reports

Patient 1

A 54-year-old woman presented to our institution in the autumn of 1998 for evaluation of metastatic FTC. A total thyroidectomy had been performed elsewhere in 1995 when FTC was diagnosed. Approximately a year later, she underwent external beam radiation therapy for intracranial metastases. On examination, she had vision defects and palsy associated with left cranial nerves III and VI. Magnetic resonance imaging (MRI) showed a larger sellar mass with chiasmal compression, sphenoid sinus involvement, clivus deformity, and pontine impingement (Fig. 1).

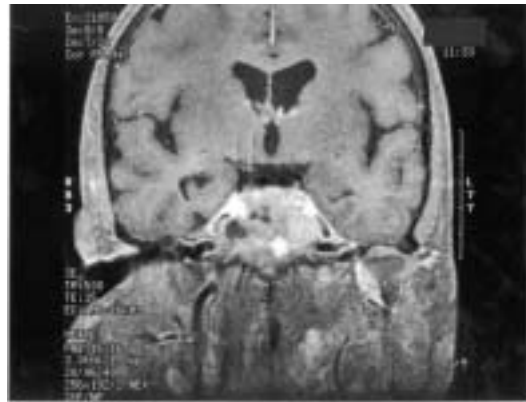


Fig. 1. Patient 1. Magnetic resonance imaging shows a large sellar mass with chiasmal compression, sphenoid sinus involvement, and clivus deformity.

No other metastases were identified from a bone scan or from other radiologic investigations. Her level of sensitive TSH (sTSH) was undetectable, with thyroglobulin (Tg) levels of 3,400 ng/mL (3,400 µg/L) in the absence of Tg antibodies. Because of the low level of

cortisol, corticosteroid therapy was begun and the patient underwent transphenoidal removal of the metastatic thyroid carcinoma. Only partial resection was possible. Surgical pathologic evaluation confirmed the diagnosis of FTC. Postoperative cessation of thyroxine therapy failed to increase serum sTSH levels (maximum sTSH, 0.019 mIU/L) despite a concentration of serum free thyroxine of 0.3 ng/dL (3.86 pmol/L). The ^{131}I WBS showed no uptake in the pituitary and only minimal uptake in the neck, consistent with known remnants of tumors in the neck. Two 0.9-mg doses of rhTSH (thyrogen) were administered intramuscularly on successive days. Repeat ^{131}I WBS showed uptake in the sellar and neck regions corresponding to known metastases. The patient was subsequently treated with 300 mCi of ^{131}I , and a post-therapy scan confirmed uptake in the sellar and neck regions (Fig. 2).

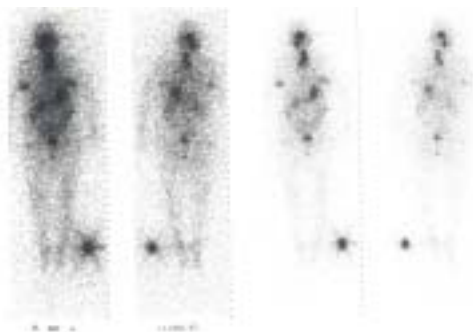


Fig. 2. Patient 1. Post-therapy scan after thyrogen stimulation confirms uptake in the sellar and neck regions.

Patient 2

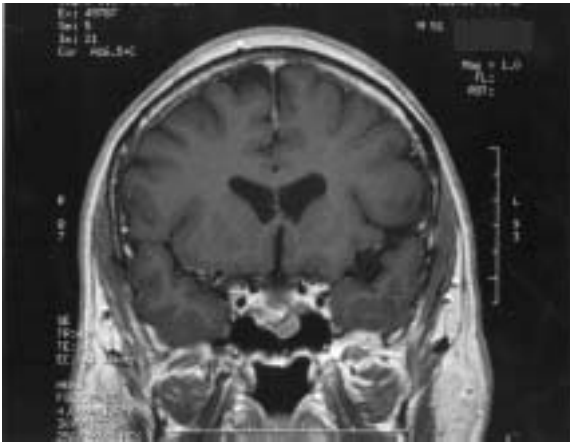
A 51-year-old man presented to our institution in the spring of 2000 for evaluation of metastatic thyroid cancer. In 1987, near total thyroidectomy was performed elsewhere for locally invasive PTC. No RAI therapy was administered at that time. In 1989, recurrent tumors in the neck were surgically removed. In early 1992, RAI treatment was instituted for local disease in the thyroid bed and neck. When the patient first presented to our insti-

tution in the autumn of 1992, further surgical removal of recurrent tumors in the thyroid bed and cervical lymph nodes was performed. At that juncture, computed tomography (CT) showed numerous tiny pulmonary nodules that were not apparent on ^{131}I WBS. Suppressive thyroxine therapy was instituted. Between 1992 and 2000, when the patient was rechecked elsewhere, levels of serum Tg gradually increased to 1,250 ng/mL (1,250 $\mu\text{g/L}$) (with Tg antibody < 20 IU/mL [20,000 IU/L]). Withdrawal of thyroid hormone therapy failed to increase the concentration of endogenous TSH on at least 1 occasion. At this point, the patient was referred to our institution for the second time.

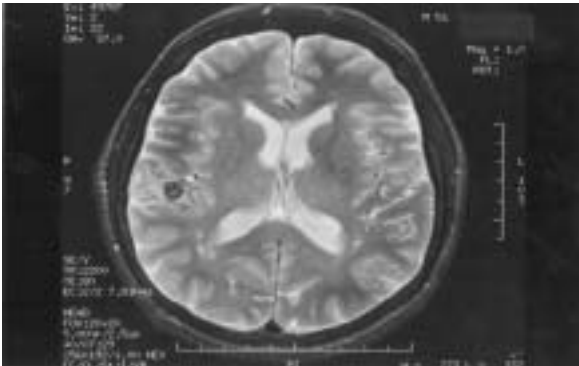
CT showed extensive recurrences in the neck and multiple tiny pulmonary lesions. The recurrent tumors in the neck were surgically debulked. No bony metastases were detected. However, MRI of the head showed intracranial lesions in the floor of the sella and in the right frontoparietal lobe (Fig. 3).

Functional tests of the pituitary revealed hypogonadotropic hypogonadism with the following concentrations of hormones: testosterone, 109 ng/dL (3.78 nmol/L); LH, 2.3 IU/L; FSH, 3.4 IU/L; and prolactin, 1.8 ng/mL (1.8 $\mu\text{g/L}$). The pituitary lesion was removed by a transphenoidal operation; then stereotactic radiosurgery with a gamma knife was performed on the right frontal lesion. The diagnosis after surgical pathologic evaluation of the pituitary lesion was null-cell adenoma. Subsequently, ^{131}I WBS after 2 doses of rhTSH showed no uptake in the cerebral region despite a concentration of sTSH of 48 mIU/L. However, development of simple partial seizures, most likely secondary to cerebral metastases and edema, precluded RAI therapy. Subsequently, after withdrawal of thyroxine therapy once again failed to increase endogenous levels of TSH, rhTSH-augmented RAI therapy was performed elsewhere. A post-therapy scan after 250 mCi of ^{131}I showed no uptake in areas of known metastases. Although rTSH made therapeutic administration of radioactive io-

dine possible but poorly differentiated papillary cancer did not accumulate radioactive iodine. Despite trans-sphenoidal resection of metastatic lesion, 2 months later, the patient died one year later from metastatic disease. This patient represents a case of Tg-positive, WBS-negative FCDC in whom attempt at therapy was possible only after administration of rhTSH.



3 A



3 B

Fig. 3. A and B, Patient 2. Magnetic resonance imaging of the head shows intracranial lesions in the floor of the sella and in the right frontoparietal lobe.

Discussion

The advent of rhTSH has made it possible to successfully treat patients with recurrent metastatic FCDC when production of endogenous sTSH is lacking because of con-

comitant pituitary or hypothalamic disorders. Until recently, the only exogenous TSH available was bovine TSH. However, use of bovine TSH has been limited because of formation of neutralizing antibodies and reports of allergic reactions, including anaphylaxis.⁵⁻⁷ With the use of rhTSH, such side effects are eliminated.

Metastases of a primary tumor to the pituitary are uncommon. In an autopsy series, the pituitary gland was a site for secondary lesions in 2% to 4% of cases with disseminated neoplasms.^{8,9} In a series of over 1,300 patients treated with a transsphenoidal operation for sellar lesions, only 1% had cancer metastatic to the pituitary gland.¹⁰ Among that 1%, breast cancer was the commonest primary tumor; next were lung cancer, colon cancer, prostate cancer, and pancreatic cancer.¹⁰⁻¹²

Cerebral metastases of FCDC are rare. In a series of 100 patients who had PTC with distant metastases and who had primary surgery in our institution from 1940 through 1989, the brain was the site of first distant metastasis in only 3% of the patients.¹³ However, the brain was the commonest site of second distant metastasis, accounting for 34% of the cases, and of subsequent metastases, accounting for 40% of the cases. Furthermore, pituitary metastasis from primary FCDC is uncommon, as evident from the analysis of our database and medical records. Of the 2,545 patients with FCDC who had primary surgery at our institution, only 19 (0.75%) had concomitant hypopituitarism, and in only 1 patient (0.04%) was the hypopituitarism due to pituitary metastasis of FCDC. As mentioned above, pituitary adenoma occurred in about half of the patients with hypopituitarism associated with FCDC. However, we may have underestimated the true number of cases of hypopituitarism because thyroid hormone therapy was not withdrawn after primary thyroid surgery for each of the 2,545 patients with FCDC.

Use of rhTSH in the treatment of FCDC is becoming more widespread. Several case reports have been published about the use of

rhTSH for the management of metastatic FCDC when the response of endogenous TSH to withdrawal of thyroxine therapy has been lacking. The reported cases include prior pituitary surgery for ACTH-secreting pituitary tumor (1), metastatic PTC (2), FTC (3), and empty sella syndrome (4). An extensive multicenter study of 229 adult patients with FCDC compared the effects of administration of rhTSH on the results of 131I WBS with the effects of withdrawal of thyroid hormone therapy on the results of 131I WBS.¹⁴ Results of the 2 scans were concordant in 89% of the patients. On the basis of a cutoff level for serum Tg of 2 ng/mL (2 µg/L), thyroid tissue or cancer was detected in 52% of patients after rhTSH stimulation and in 56% of patients after withdrawal of thyroid hormone therapy in those with disease or thyroid tissue limited to the thyroid bed. However, using the same cutoff level for Tg, a combination of radioiodine whole body scan and serum Tg after rhTSH stimulation detected thyroid tissue or cancer in 93% of patients with disease or tissue limited to thyroid bed and 100% of patients with metastatic disease. Adverse effects were limited to transient headaches in 9% of patients and nausea in 6%; the incidence of adverse effects was no different between the 2 diagnostic procedures.

However, a recent report mentions the development of hemiplegia 48 hours after ad-

ministration of rhTSH in a patient with pituitary metastasis of a primary FCDC.¹⁵ Although cerebral edema and hemorrhage have been associated with 131I therapy in patients with cerebral metastases,¹⁶ in this report, hemiplegia occurred before the institution of RAI therapy, suggesting a causal link. Besides, TSH, whether derived endogenously or exogenously, is a trophic hormone that could potentially contribute to tumor growth, although this hypothesis remains unproven. However, exogenously administered rhTSH is more likely to result in transient elevation of concentrations of serum TSH as compared with the prolonged elevation of concentrations of TSH that occurs after withdrawal of thyroid hormone therapy. Therefore, despite the reported case of hemiplegia, rhTSH-stimulated 131I scans would be favored over scans after withdrawal of thyroid hormone therapy as a means to reduce the potential morbidity of prolonged hypothyroidism and consequent risk of tumor growth in metastatic disease of the central nervous system.

Although metastasis of FCDC to the pituitary is rare as shown by our study, association of pituitary insufficiency with FCDC is more common. The availability of rhTSH is an advance in therapy for patients with deficient reserve of endogenous TSH.

References

1. Ringel MD, Ladenson PW. Diagnostic accuracy of 131I scanning with recombinant human thyrotropin versus thyroid hormone withdrawal in a patient with metastatic thyroid carcinoma and hypopituitarism. *J Clin Endocrinol Metab.* 1996; 81(5): 1724-5.
2. Masiukiewicz US, Nakchbandi IA, Stewart AF, Inzucchi SE. Papillary thyroid carcinoma metastatic to the pituitary gland. *Thyroid.* 1999; 9(10): 1023-7.
3. Risse JH, Grunwald F, Bender H, Schuller H, Van Roost D, Biersack HJ. Recombinant human thyrotropin in thyroid cancer and hypopituitarism due to sella metastasis. *Thyroid.* 1999; 9(12): 1253-6.
4. Colleran KM, Burge MR. Isolated thyrotropin deficiency secondary to primary empty sella in a patient with differentiated thyroid carcinoma: an indication for recombinant thyrotropin. *Thyroid.* 1999; 9(12): 1249-52.
5. Hays MT, Solomon DH, Beall GN. Suppression of human thyroid function by antibodies to bovine thyrotropin. *J Clin Endocrinol Metab.* 1967; 27(11): 1540-9.
6. Sherman wb, Werner sc. Generalized allergic reaction to bovine thyrotropin. *Jama.* 1964 19; 190: 244-5
7. Melmed S, Harada A, Hershman JM, Krishnamurthy GT, Bland WH. Neutralizing antibodies to bovine thyrotropin in immunized patients with thyroid cancer. *J Clin Endocrinol Metab.* 1980; 51(2): 358-63.

8. Molinatti PA, Scheithauer BW, Randall RV, Laws ER Jr. Metastasis to pituitary adenoma. *Arch Pathol Lab Med.* 1985; 109(3): 287-9.
9. Max MB, Deck MD, Rottenberg DA. Pituitary metastasis: incidence in cancer patients and clinical differentiation from pituitary adenoma. *Neurology.* 1981; 31(8): 998-1002.
10. Branch CL Jr, Laws ER Jr. Metastatic tumors of the sella turcica masquerading as primary pituitary tumors. *J Clin Endocrinol Metab.* 1987; 65(3): 469-74.
11. Teears RJ, Silverman EM. Clinicopathologic review of 88 cases of carcinoma metastatic to the pituitary gland. *Cancer.* 1975; 36(1): 216-20.
12. Roessmann U, Kaufman B, Friede RL. Metastatic lesions in the sella turcica and pituitary gland. *Cancer.* 1970; 25(2): 478-80.
13. Dinneen SF, Valimaki MJ, Bergstralh EJ, Goellner JR, Gorman CA, Hay ID. Distant metastases in papillary thyroid carcinoma: 100 cases observed at one institution during 5 decades. *J Clin Endocrinol Metab.* 1995; 80(7): 2041-5.
14. Haugen BR, Pacini F, Reiners C, Schlumberger M, Ladenson PW, Sherman SI, et al. A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. *J Clin Endocrinol Metab.* 1999; 84(11): 3877-85.
15. Vargas GE, UY H, Bazan C, Guise TA, Bruder JM. Hemiplegia after thyrotropin alfa in a hypothyroid patient with thyroid carcinoma metastatic to the brain. *J Clin Endocrinol Metab.* 1999; 84(11): 3867-71.
16. Holmquest DL, Lake P. Sudden hemorrhage in metastatic thyroid carcinoma of the brain during treatment with iodine-131. *J Nucl Med.* 1976; 17(4): 307-9.