TSH-Secreting Pituitary Adenoma: Current Management and Review

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ABSTRACT—The neurosurgical literature contains little information about the current management of patients with thyroid-stimulating hormone (TSH)-secreting pituitary adenomas or about the usefulness of the somatostatin analogue octreotide in such cases. While TSH-secreting pituitary adenomas are rare, our review and illustrative case demonstrate the effectiveness of pretreating patients with octreotide therapy not only to reduce tumor size prior to surgical resection but also to increase the possibility of clinical remission.

A 52-year-old male presented with signs and symptoms of hyperthyroidism and elevated TSH, thyroxine, and triiodothyronine. Magnetic resonance imaging revealed a pituitary macroadenoma with extension into the suprasellar cistern. The patient was treated with octreotide for 6 months prior to surgery. Approximately 3 months after initiation of octreotide therapy, the patient exhibited excellent biochemical and clinical response. Tumor shrinkage of nearly 50% was associated with resolution of suprasellar extension and optic nerve compression. Subsequent transsphenoidal surgery for resection of residual adenoma was followed by symptomatic and hormonal remission without the need for reinstitution of octreotide therapy.

Pretreatment with octreotide for TSH-secreting pituitary adenomas has a beneficial effect on disease symptoms and reduces tumor mass. We suggest that patients with these rare tumors can be managed with a combination of octreotide therapy and subsequent surgical removal of residual tumor. Although this combination treatment helps to facilitate clinical remission, only short-term follow-up has been reported and thus the optimal management of these patients remains to be determined.

Surgical resection remains the basis for definitive treatment of thyroid-stimulating hormone (TSH)-secreting pituitary adenomas.¹⁻³ These rare tumors comprise 1 to 2.8% of all pituitary adenomas and are typically invasive neoplasms.^{3,4} The combination of surgery and radiotherapy has achieved short-term cures in approximately 41 to 46% of patients, but these reports included follow-up from only 3 to 36 months.^{3,5}

Information on the current management of TSH-secreting pituitary adenomas is scarce in the neurosurgical literature. However, a review of all literature revealed that long-acting somatostatin analogues have proven to be an

effective adjunct therapy for TSH-secreting pituitary adenomas. Octreotide has been shown to reduce TSH secretion in almost all cases, normalize thyroid hormone levels in three-fourths of cases, and shrink tumors in up to one-third of patients receiving long-term treatment.^{1,6,7}

This review includes a report of a unique case of a TSH-secreting pituitary adenoma to illustrate the dramatic effect of pretreatment with octreotide therapy on clinical symptomatology, TSH levels, thyroid hormone levels, and tumor volume. While a combination of octreotide pretreatment followed by surgical resection led to clinical remission in our patient, it remains to be de-

terminated whether this current management technique will improve the long-term outcome.

CASE REPORT

A 52-year-old white male with a 7-year history of scleroderma was referred for evaluation and management of hypogonadotropic hypogonadism. The patient complained of hot flashes, hair loss, and decreased libido and erectile function. In addition, he had lost 28 pounds over the preceding 18 months. He denied headache or visual disturbance. On physical examination, he had a diffusely enlarged thyroid gland, but no signs of ophthalmopathy or dermatopathy. Neurologically he was normal with full visual fields. Hormonal analysis revealed elevated TSH (6.16 to 11.44 $\mu\text{IU/mL}$), free thyroxine index (12.5 to 21.4 $\mu\text{g/dL}$), and triiodothyronine (T_3) (363 to 525 ng/dL). Magnetic resonance imaging (MRI) demonstrated a pituitary macroadenoma with extension into the suprasellar cistern and optic chiasm compression, as well as possible invasion but certain encroachment of the cavernous sinuses more pronounced on the left side (Fig. 1).

The patient was started on propylthiouracil therapy (100 mg orally, three times daily) and testosterone (Depo-Testosterone, 300 mg intramuscularly every 4 weeks). Several weeks later, in May 1995, an indium-111 octreoscan showed a 0.11% uptake per 24 hours. Propylthiouracil therapy was stopped and octreotide therapy (100 μg subcutaneously every 8 hours) was begun. By late

June the patient noted improvement in his hypogonadal symptoms and had gained 11.7 pounds. Octreotide therapy had resulted in euthyroidism with normalization of TSH (0.36 to 4.80 $\mu\text{IU/mL}$), T_3 (139 to 172 ng/dL), and free thyroxine index (4.84 to 6.4 $\mu\text{g/dL}$). In August, 3 months after initiation of octreotide therapy, repeat MRI revealed marked tumor shrinkage of approximately 50% with complete resolution of all suprasellar extension (Fig. 2). A repeat indium-111 octreoscan demonstrated a 50% decrease in uptake to 0.056% per 24 hours. The patient was treated for an additional 4 months with octreotide, remaining euthyroid.

In October 1995, a repeat MRI failed to demonstrate further shrinkage of the adenoma. Because of the lack of further decrease in tumor size, the cost and inconvenience of thrice daily injections, and the belief that surgical resection might decrease or obviate continued therapy, transsphenoidal resection was elected.

In December 1995, gross resection of the pituitary adenoma was undertaken. During the operation the yellow-tan adenoma was found to be slightly tougher than usual but of average vascularity without signs of hemorrhage. After exploration, the diaphragma sellae, the medial walls of the cavernous sinuses, and the floor of the sella were clear of tumor and the diaphragma sellae had descended well into the sella.

Immunoperoxidase stains revealed strong reactivity with TSH and chromogranin antisera, weak reactivity to follicle-stimulating hormone (FSH), and no reactivity with anti-luteinizing hormone. A biopsy of the anterior sellar dura proved positive for microinvasion. The patho-

Figure 1. (A). Coronal magnetic resonance (MR) image depicting the pituitary adenoma with elevation of the optic chiasm. Enhancement extends bilaterally above the carotid artery and indicates probable cavernous sinus invasion (1 = optic chiasm, 2 = cavernous sinus invasion). (B). Mid-sagittal MR image of adenoma (= 1).

Figure 2. (A). Coronal MR image demonstrates the shrinkage of the adenoma 3 months after treatment with octreotide. Pituitary stalk (= 1) and optic chiasm (= 2) are now visible. (B). Sagittal MR image after octreotide treatment. Note the optic chiasm is now completely decompressed (= 1).

logical diagnosis was that of a plurihormonal TSH, FSH adenoma.

Repeat MRI in February 1996 revealed a significant decrease in size of the tumor (Fig. 3). Enhancing tissue extending up to and possibly into the cavernous sinus was still apparent. Nine months after surgery and discontinuation of octreotide and antithyroid medications, the patient remained clinically euthyroid (TSH

0.56 μ IU/mL, free thyroxine index 4.9 μ g/dL, and T_3 99 ng/dL).

DISCUSSION

Since the advent of TSH monoclonal antibodies in the mid-1980s and immunometric assays, the diagnosis

Figure 3. (A). Coronal MR image 2 months after transsphenoidal resection of the adenoma. The enhancing tissue remains around the carotid arteries and suggests residual disease in the cavernous sinus despite normalization of serum hormonal levels. (B). Sagittal MR image 2 months after transsphenoidal resection.

of TSH-secreting pituitary adenomas has been recognized more frequently. In 1960, Jailer and Holub postulated that a pituitary tumor could be the source of excessive quantities of TSH responsible for thyrotoxicosis.⁸ Ten years later, Hamilton et al. were credited with reporting the first case of a TSH-secreting pituitary adenoma.⁹ Currently, there are more than 140 cases in the literature and the characteristics of TSH-secreting pituitary adenomas are well described. Typically, patients present with hyperthyroid symptoms and elevated T_4 and T_3 levels but normal to elevated TSH levels. Ophthalmopathy or dermopathy is usually not present. Imaging studies of the sella generally reveal a pituitary macroadenoma. The large and invasive qualities of these tumors at diagnosis have generally been attributed to a delay in diagnosis. Thyroidectomy or end organ ablation is generally contraindicated and may disinhibit the pituitary tumor and induce more aggressive growth suggestive of the clinical scenario for patients with Nelson's syndrome.² Antithyroid medications are also postulated to have similar disinhibitory effects on the primary pituitary tumor. The invasive nature of these tumors renders them difficult to excise completely and they are relatively radioresistant.^{2,3}

Long-acting somatostatin analogues have been remarkably effective for TSH-secreting pituitary adenomas. Somatostatin-related peptides constitute a family that includes somatostatin 14, somatostatin 28, and several larger prohormone forms.¹⁰ This family of related peptides is found and synthesized in the central nervous system, peripheral nervous system, pancreatic islet D-cells, and the epithelial glandular and neuronal cells of the gastrointestinal tract. They can act as neurotransmitters, local hormones, systemic hormones, autocrine agents, or paracrine agents that inhibit the secretion of other hormones or cell products.¹¹ Somatostatin acts to inhibit the tonic and phasic secretion of growth hormone and thyrotropin by the anterior pituitary. Several mechanisms of action have been postulated for the inhibition of TSH, involving cAMP levels, intracellular Ca^{+2} concentrations, and somatostatin binding sites coupled to inhibitory G-proteins.⁵ Somatostatin has been shown to inhibit adenylate cyclase and reduce cAMP levels in direct relation to the amount of somatostatin binding sites. Other mechanisms independent of cAMP levels relate to somatostatin-induced membrane hyperpolarization causing decreased intracellular Ca^{+2} in the thyrotrope cells which in turn reduces TSH secretion.¹²

Because of a short serum half-life of approximately 2 minutes, somatostatin was not used therapeutically until the development of the long-acting somatostatin analogue octreotide. The elimination half-life of octreotide is 1.5 hours and duration of action is up to 12 hours. Subsequently, octreotide has been shown to be effective in controlling hypersecretion of thyrotropin and the associated hyperthyroidism due to TSH-secreting pituitary adenomas.¹³ Some authors advocate that octreotide therapy should be considered first-line treatment for inoperable

cases.^{7,11,13,14} Chanson et al. demonstrated the biochemical and clinical efficacy of octreotide therapy in a follow-up study of 52 patients with TSH-secreting pituitary adenomas. In their study, thyroid hormone levels were reduced in all patients and returned to normal in 73%.^{6,7}

Interestingly, octreotide has not been shown to be as reliable for tumor shrinkage. Although improvement in chiasmal dysfunction with use of octreotide was reported in 1987,¹⁵ in 1991 Warnet et al. were the first to report undisputable tumor shrinkage of a primary TSH-secreting pituitary adenoma by octreotide therapy.¹⁴ Chanson et al. observed partial tumor shrinkage in 10 of 25 patients receiving long-term therapy (>3 months) as assessed by computed tomography or MRI. Another patient showed reduced tumor volume after only 20 days of therapy.^{6,7} The 11 patients in Chanson's review consisted of various case reports^{14,16-20}; however, on close review, the patient reported by Wemeau et al.²⁰ actually demonstrated no diminution in tumor volume. Orme et al. reported an additional patient with a TSH-secreting pituitary adenoma exhibiting marked tumor shrinkage after just 2 weeks of therapy.²¹

Our patient is the 13th reported case of documented tumor shrinkage after octreotide therapy. Of these 13 patients, 9 demonstrated a 30 to 70% reduction in tumor volume and 4 patients had minor or unspecified tumor shrinkage. The average dose of octreotide was 100 μ g administered subcutaneously every 8 hours. The course of treatment before tumor shrinkage was noted ranged from 2 weeks to 18 months. Information on 5 of the 13 patients regarding subsequent surgical management revealed that 4 patients underwent gross resection and 1 patient underwent subtotal surgical debulking after pretreatment with octreotide. Half of the patients with gross removal were cured and the other half had clinical relapse of their hyperthyroidism. Unfortunately, follow-up was not reported beyond 3 years. These reports of case series represent retrospective, uncontrolled reviews with relatively short follow-up and therefore conclusions regarding the ultimate impact of pretreatment of these tumors with octreotide and the optimal management of these patients must remain the bias of the treating physician.

Our patient's course illustrates the beneficial effect of octreotide on disease symptoms, thyroid hormone levels, and tumor volume, possibly facilitating surgical removal and clinical remission. The duration of remission has yet to be seen and radiation therapy may have to be considered in the future. This combination therapy, however, represents a useful management paradigm for treatment of patients with these rare tumors.

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