Thyrotrophin (TSH)-Secreting Pituitary Macroadenoma with Cavernous Sinus Invasion

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ABSTRACT

Thyrotrophin (TSH)-secreting pituitary adenomas, although rare, should be recognised as a possible cause of normal or elevated serum TSH in the presence of elevated serum free thyroid hormone levels. Clinical hyperthyroidism may be mild or absent. Early recognition provides the best chance for surgical cure. We report a patient with a TSH-secreting pituitary tumour with cavernous sinus invasion. This case illustrates that multiple modalities of treatment are often necessary and complementary in achieving control of tumour growth and hormonal hypersecretion when these tumours are diagnosed late.

Keywords: Thyrotrophin-secreting tumour, pituitary macroadenoma, gamma-knife radiosurgery, somatostatin analogues

Singapore Med J 2001 Vol 42(9):433-437

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INTRODUCTION

Thyrotrophin (TSH)-secreting pituitary adenomas are a rare cause of hyperthyroidism. They account for 1-3% of all functioning pituitary tumours and much less than 1% of all cases of hyperthyroidism[1,2]. Because of their usually aggressive nature and the fact that hyperthyroidism is often mistaken for other more common causes of thyrotoxicosis, the diagnosis of TSH-secreting adenoma is often delayed until the tumours become large and invasive. Hence, surgical removal is usually incomplete and even after additional pituitary irradiation, only about 40% of patients may be cured[1]. We describe a patient with this rare pituitary tumour with cavernous sinus invasion, his clinical course and response to multi-modality therapy.

CASE REPORT

A 52-year-old male executive, who had apparently been suffering from anxiety and depression for many years, presented with increasing headaches since 1999. These headaches were frequently midfrontal or generalised, were present on awakening in the morning and could last all day except when he was distracted by work. He had lost 4 kg in weight between 1997 and 1999. He had a history of chronic insomnia managed with tranquilisers and occasional periods of excessive anxiety for many years, which became worse since 1997. His severe headache prompted him to seek medical consultation with his family physician.

On clinical examination he appeared anxious. His body mass index (BMI) was within the normal range at 22.4 kg/m^2. (Height 1.65 m, weight 61 kg). His palms were sweaty, but he claimed that this was long standing. The blood pressure was 150/100 mmHg and the pulse was 90/min with a regular rhythm. He exhibited no other signs of thyrotoxicosis and there was no goitre. Visual acuity and fundoscopic examination were also normal. A magnetic resonance imaging (MRI) of the brain revealed a pituitary macroadenoma to the right of the midline, measuring 1.7 x 2.0 x 2.0 cm, displacing the optic chiasm superiorly, invading the right cavernous sinus and partly encasing the right carotid artery (Fig. 1). A thyroid screen showed an elevated serum free T4 level of 33.7 pmol/L (N: 11.6-27.0 pmol/L) with an inappropriately elevated serum TSH of 7.04 mU/L (N: 0.50-4.50 mU/L). He was then referred to endocrinologist for further evaluation.

Repeat thyroid panel performed at a different laboratory confirmed the suspicion of central hyperthyroidism with serum free T4 of 29.0 pmol/L (N: 10.0-20.0 pmol/L) and serum TSH 5.27 mU/L (N: 0.45-4.50 mU/L). The rest of the pituitary function was essentially normal: serum prolactin 0.40 nmol/L (N: 0.16-0.65 nmol/L); 9 am serum cortisol 153 nmol/L (N: 138-689 nmol/L); 9 am plasma ACTH 16.0 mU/L (N: 10.0-46.0); 24 hour urine free cortisol 111 nmol/day (N: 27-221 nmol/day); serum testosterone 24.1 nmol/L (N: 9.4-37.0 nmol/L). Visual field examination by Octopus perimeter showed early bilateral superior temporal relative scotoma.

A week later (June 1999), he underwent transsphenoidal resection of the pituitary tumour. Pathology revealed an adenoma staining positive for TSH and FSH much more than LH and GH. The tumour cells were negative for ACTH and prolactin. Following surgery, his visual field remained stable but

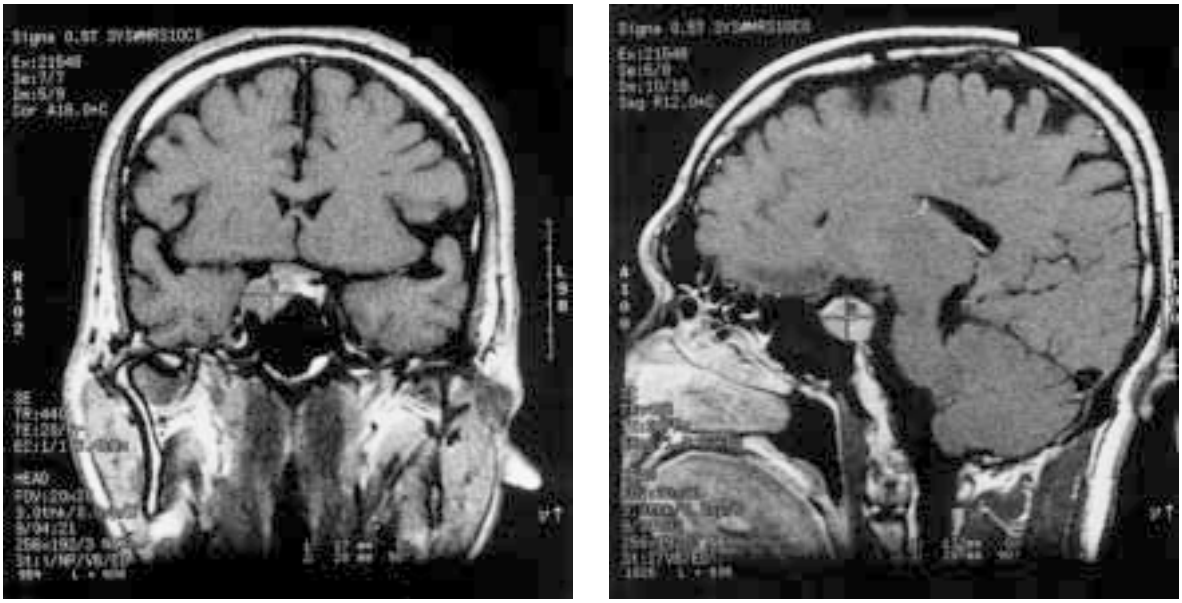

Fig. 1 Coronal (left panel) and sagittal (right panel) views of pituitary gland showing a large tumour (crosses) displacing the optic chiasm superiorly and partly encasing the carotid artery on the right side.

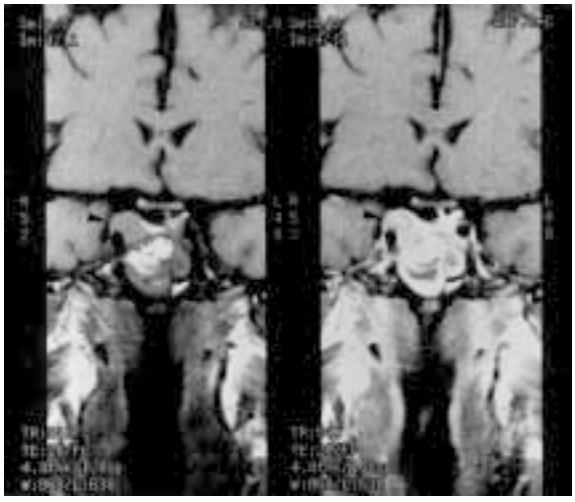

Fig. 2 Unenhanced (left) and enhanced (right) coronal views of pituitary gland showing remnant tumour (arrowheads) closely related to the carotid siphon but well clear of the optic chiasm after the first transsphenoidal surgery.

he continued to have daily headaches. Serial thyroid panel still showed borderline-high levels of serum free T4 with non-suppressed TSH concentrations (Table I). The remainder of his pituitary hormone testing remained within normal limits. Post-operative MRI in August 1999 showed a 1.5 x 1.3 x 1.8 cm remnant enhancing pituitary tumour closely related to the right carotid siphon, extending up toward the right optic nerve (Fig. 2).

The patient was given an option of repeat surgery, radiation therapy and medical therapy to control tumour growth and TSH hypersecretion. He opted for medical therapy and was commenced on subcutaneous injections of octreotide 50 μg thrice daily. Although this normalised his thyroid function and improved his weight, he tolerated octreotide injections poorly with complaint of worsening headaches. He stopped his injections after six weeks, resulting in relapse of biochemical hyperthyroidism (Table I). He was then given a trial of tab cabergoline 0.5 mg at bedtime once weekly; this was again discontinued shortly because of insomnia and worsening headaches.

He was then referred to the University of Virginia Health System, USA, for a repeat transsphenoidal surgery in May 2000. The neurosurgeon successfully debulked the tumour within the pituitary fossa, leaving only a nodular portion within the cavernous sinus measuring 1.0 x 1.0 x 0.6 cm. (volume 1.6 cm^3). Histology revealed a pituitary adenoma with diffuse cytoplasmic immunoreactivity for TSH and α-subunit of the glycoprotein. Post-operatively, his serum TSH levels fell successively over the next three days from 3.44 to 0.57, 0.45 and 0.39 mU/L, respectively (Table I). He was given oral hydrocortisone replacement on discharge as his morning serum cortisol level was 57 nmol/L after withdrawal of steroids administered intra-operatively; whereas measurements of serum free T4, T3, TSH, FSH, LH, prolactin and testosterone concentrations respectively showed results within the normal ranges. One week post-operatively, he had adjuvant gamma-knife treatment to the remnant tumour within the right cavernous sinus.

Because of the aggressive nature of the tumour and it would be some time before the gamma-knife therapy is fully effective, he was offered long-acting octreotide LAR as interim medical therapy since he had demonstrated biochemical response to octreotide treatment previously. To minimise the side effects, the dose of long-acting octreotide LAR was gradually titrated upwards to 30 mg once a month.

Table I. Thyroid function results of patient with TSH-secreting pituitary adenoma during follow-up.

Date	fT4 (pmol/L)	Reference range	TSH (mU/L)	Reference range
21.05.99	33.7	11.6 - 27.0	7.04	0.50 - 4.50
25.05.99	29.0	10.0 - 20.0	5.27	0.45 - 4.50
01.06.99	30.7	9.0 - 24.0	5.73	0.50 - 4.50
02.06.99	Initial transsphenoidal surgery			
12.06.99	ND	–	1.37	0.50 - 4.50
14.06.99	24.6	9.0 - 24.0	ND	–
22.06.99	22.1	9.0 - 24.0	1.83	0.50 - 4.50
26.07.99	23.6	10.0 - 20.0	5.07	0.45 - 4.50
24.08.99	25.8	11.6 - 27.0	4.08	0.50 - 4.50
08.12.99	25.0	10.0 - 20.0	2.55	0.40 - 3.98
18.12.99 - 01.02.00	Octreotide treatment (SC Sandostatin® 50ug t.i.d.)			
12.01.00	16.0	10.0 - 20.0	2.02	0.40 - 3.98
28.02.00	25.0	10.0 - 20.0	4.56	0.40 - 3.98
01.03.00 - 05.04.00	Dopamine agonist treatment (oral cabergoline 0.5mg weekly)			
03.04.00	22.0	10.0 - 20.0	3.91	0.40 - 3.98
17.05.00	158 nmol/L*	58 - 140	3.44	0.40 - 6.00
18.05.00	Repeat transphenoidal surgery			
19.05.00	ND	–	0.57	0.40 - 6.00
20.05.00	ND	–	0.45	0.40 - 6.00
21.05.00	ND	–	0.39	0.40 - 6.00
25.05.00	Gamma-knife radiosurgery			
26.05.00	121 nmol/L*	58 - 140	0.53	0.40 - 6.00
13.06.00	12.1	10.0 - 20.0	0.94	0.45 - 4.50
04.07.00	11.2	10.0 - 20.0	1.52	0.45 - 4.50
12.08.00	Initiation of Sandostatin LAR® monthly injections			
11.09.00	8.0	10.0 - 20.0	1.01	0.45 - 4.50
09.10.00	8.9	10.0 - 20.0	1.04	0.45 - 4.50
13.12.00	12.0	10.0 - 20.0	2.14	0.45 - 4.50

* Total T4 instead of free T4 measurement
ND: Not done

When last reviewed in December 2000 (seven months post repeat surgery), he tolerated the treatment relatively well except for complaint of transient headaches in the morning that cleared during working. Laboratory tests performed showed normal thyroid function (Table I) and some return of corticotroph function, as his morning serum cortisol was 325 nmol/L when drawn more than 24 hours after his last hydrocortisone dose. A short Synacthen test would be performed at the next visit to assess if his hydrocortisone replacement could be discontinued. Although there is no evidence of recurrence biochemically or on the MRI, the patient would be treated with long-acting octreotide LAR at least for a year so as to suppress any residual tumour cells before the gamma-knife therapy becomes effective.

DISCUSSION

The biochemical hallmark of a TSH-secreting pituitary adenoma (TSH-oma) is an inappropriately elevated serum immunoreactive TSH level in the presence of high free thyroid hormone concentrations, reflecting autonomous TSH secretion. In overt primary hyperthyroidism, serum TSH levels should be undetectable using 3rd generation TSH assays (<0.01 mU/L); detectable TSH in the presence of elevated free T4 and/or T3 concentrations distinguishes central from primary forms of hyperthyroidism. Before the advent of ultra-sensitive TSH assays, these tumours were frequently misdiagnosed as non-functioning pituitary adenomas[3].

In patients with inappropriately elevated TSH levels, however, it is important to exclude drugs, acute illness, abnormalities of thyroid hormone protein binding or auto-antibodies to thyroid hormones, as a possible cause of the syndrome of euthyroid hyperthyroxinaemia with inappropriate TSH elevation. When these have been ruled out, two rare causes need to be considered: TSH-secreting pituitary adenoma (TSH-oma) or resistance to thyroid hormone syndrome (RTH).

Special laboratory tests that may help distinguish TSH-omas from RTH include the finding of elevated levels of serum α-subunit of pituitary glycoprotein hormones (α-PGH>1.2 ng/mL), serum α-PGH to TSH molar ratio (α-PGH:TSH>1), and serum sex-hormone binding globulin, respectively. Using dynamic testing in patients with TSH-omas, serum TSH will not increase with thyrotrophin releasing hormone (TRH) stimulation, nor suppress in response to T3 loading[4-6]. However, in view of the unequivocal finding of a large pituitary mass lesion and the absence of thyroid dysfunction in the family, we could quite confidently make a diagnosis of TSH-oma in our patient.

A recent review summarised the findings in 280 patients with TSH-secreting adenomas[4]. The mean age at presentation was 41 years and 55% were women. In patients with TSH-omas, hyperthyroid symptoms may be mild or subtle and not uncommonly overshadowed by features arising from the expanding tumour mass, since about 90% are macroadenomas. Our patient had headache, probably from dural invasion by tumour, as his presenting complaint. In the pooled clinical series, visual field defects were reported in about one-half, headache in one-sixth, and menstrual disturbances in one-third of patients[4].

About 95% of patients with TSH-oma have a diffuse goitre, although goitre was not detectable in our patient. Before the advent of ultra-sensitive TSH assays, treatment was often erroneously targeted at the thyroid gland, either with anti-thyroid drugs or ablative therapy, but the hyperthyroidism or goitre was usually recurrent or persistent. If the thyroid was totally ablated, TSH levels would remain

inappropriately elevated despite an adequate or even supra-physiologic doses of thyroid hormone[3]. More importantly, invasive macroadenomas have been found to be twice as common in patients who had unwittingly undergone thyroid ablation. Indeed, previous thyroid ablation may promote aggressive transformation of the pituitary tumour, akin to Nelson's syndrome seen after bilateral adrenalectomy for Cushing's disease[4]. Although lowering of thyroid hormone levels may promote tumour growth, maintaining thyroid hormone levels in the high-normal range does not inhibit tumour growth.

The first line therapy for patients with TSH-oma is transsphenoidal resection of the tumour. The importance of early diagnosis of functional pituitary tumours cannot be over-emphasised, since surgery achieves speedy remission of hormone hypersecretion in 70-90% of cases if diagnosed in the microadenoma stage, while the success rate falls drastically to 10-30% by the time extra-sellar extension occurred[7]. Moreover, surgically related complications increase with the size of tumour[3].

Our patient became biochemically euthyroid after repeat surgery; but this was clearly non-curative as the tumour had invaded the cavernous sinus and encased the internal carotid artery. Most experts now agree that cure should not be defined by mere euthyroidism or even absence of visible tumour on imaging[8,9]. In patients who are hyperthyroid before surgery, undetectable TSH levels measured within one week after surgery predicts surgical cure[8]. As normal thyrotrophs are still suppressed during this period, any detectable TSH should reflect tumoral TSH secretion. This assumption probably holds true for our patient despite the mild biochemical hyperthyroidism pre-operatively, with his early detectable TSH levels post surgery reflecting residual tumour. In patients with no biochemical and imaging evidence of tumour post surgery, T3 suppression test may be performed at three to six months when normal thyrotrophs should have adequately recovered. The subject is considered cured if T3 suppression leads to a complete inhibition of both basal and TRH-stimulated TSH secretion[4,8,9].

Radiotherapy, whether conventional or gamma-knife, has been shown to be effective in inhibiting residual tumour regrowth, which must be a primary aim in patients with invasive macroadenomas. For invasive pituitary tumours that are inaccessible for complete surgical excision, gamma-knife radiosurgery now provides an excellent adjunct therapy post surgery[10,11]. Whereas in conventional fractionated radiotherapy, the dose of radiation that can be safely delivered is limited because nearby critical structures are included within the radiation field, with gamma-knife, a high radiation dose that is shaped to conform closely to the tumour volume is delivered in a single session. However, there are as yet no studies documenting the long-term efficacy of gamma-knife in patients with TSH-omas; although experience with acromegaly suggests that normalisation of biochemistry occurs considerably faster with gamma-knife radio-surgery than with fractionated radiotherapy[12].

Given that native somatostatin inhibits TSH secretion, the longer acting somatostatin analogues octreotide and recently lanreotide, have been found to be useful in treating patients with a TSH-oma who have failed to achieve cure following transsphenoidal surgery and radiotherapy[4,13,14]. TSH levels almost always decrease within hours of a single parenteral injection of octreotide, while thyroid hormones normalise in about 75% of patients after one month. Tumour size is either stabilised, or shrinks in about half of patients by 30-70% after long term octreotide therapy, usually by three months[13]. However, somatostatin analogues are efficacious only for as long as they are being administered. Hormone levels and tumour size will return to pre-treatment status once the drug is discontinued, even after extended treatment periods[13]. Relapse of hyperthyroidism was seen in our patient after stopping octreotide. Notably, the introduction of slow-release formulations like long-acting octreotide LAR obviates the inconvenience associated with multiple daily injections.

Dopamine agonist therapy has proven effective only in occasional patients with a TSH-oma, usually those with concomitant hyperprolactinaemia[4,15]. In a recent case report on a young women with a pure TSH-secreting pituitary macroadenoma, bromocriptine therapy at 30 mg per day led to substantial and sustained reduction of TSH levels, as well as considerable reduction in tumour size[16]. Since dopamine agonists are given orally and are relatively inexpensive, a therapeutic trial may be advocated before one uses somatostatin analogues in patients with TSH-omas, especially in those without significant chiasmal compression. Unfortunately, we could not assess the efficacy of cabergoline treatment in our patient due to his apparent intolerance to the drug.

CONCLUSION

In summary, TSH-secreting pituitary adenomas should be considered as a possible cause of persistent inappropriate elevation of TSH when other causes have been excluded. TSH-omas tend to be more aggressive than other pituitary tumours. Clinical hyperthyroidism may be mild or absent. By the time symptoms of mass effect appear, these tumours would have expanded beyond the boundaries of the

sella turcica and the best chance for surgical cure missed. For tumours that have invaded the cavernous sinus, debulking transsphenoidal surgery followed by gamma-knife radiosurgery, if not contraindicated, seems the best therapeutic strategy. Somatostatin analogues or dopamine agonists may be employed to control biochemical hyperthyroidism and tumour growth before the effect of radiotherapy is fully accrued.

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