Long term treatment of a thyrotropin-secreting microadenoma with somatostatin analogues

Tratamento de longa duração com análogos da somatostatina de um microadenoma tirotrofinoma

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SUMMARY

Thyrotropin (TSH) secreting pituitary adenomas (TSH-omas) account for < 1% of all pituitary adenomas and are a rare cause of hyperthyroidism. The diagnosis is often made at the stage of macroadenoma because of the aggressive nature of the tumor and due to the fact that patients are mistakenly treated for more common primary hyperthyroidism for a long time. First line therapy is transsphenoidal resection of the tumor, which can cure one-third of the patients completely. However, if surgery is not possible or curative, pituitary radiotherapy and/or somatostatin analogs (SSA) can be useful. We report the case of a 54-year-old woman treated 20 years earlier for a mistakenly suspected primary hyperthyroidism. Given the persistence of symptoms she was studied further and was diagnosed with a thyrotropinoma. Despite the delay in diagnosis and prior thyroid ablation, a microadenoma was found. As transsphenoidal surgery was not considered effective, medical therapy with a somatostatin analogue was initiated. Currently, at four years of follow-up, the patient continues on this treatment and remains euthyroid and asymptomatic. We report a case of successful long-term treatment with SSA, after unsuccessful surgery. Arq Bras Endocrinol Metab. 2010;54(5):502-6

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SUMÁRIO

Tirotrofinomas (TSH-omas) representam < 1% dos adenomas hipofisários. Eles são uma causa muito rara de hipertireoidismo. O diagnóstico é frequentemente feito na fase de macroadenoma em consequência da natureza agressiva do tumor e do feito de que os doentes são tratados inicialmente por engano e por um longo tempo para hipertireoidismo primário. A terapêutica de primeira linha é a ressecção transesfenoidal do tumor, que cura um terço dos pacientes completamente. Contudo, se a cirurgia não for possível ou curativa, a radioterapia da pituitária e/ou o tratamento com análogos da somatostatina (SSA) podem ser úteis. Relatou-se o caso de uma mulher de 54 anos, tratada há 20 anos por uma suspeita equivocada de hipertireoidismo primário. Dada a persistência dos sintomas, foram realizados mais exames e a paciente foi diagnosticada com TSH-oma. Apesar do diagnóstico tardio e da ablação prévia com iodo radioativo, encontrou-se um microadenoma. Como a cirurgia transesfenoidal não foi considerada eficaz, iniciou-se o tratamento da paciente com SSA. Atualmente, após quatro anos de acompanhamento, a paciente continua com o tratamento e permanece eutireoidea e assintomática. Neste artigo, relatou-se a eficácia da terapia medicamentosa com SSA em longo prazo, após cirurgia não eficaz. Arq Bras Endocrinol Metab. 2010;54(5):502-6

INTRODUCTION

Thyrotropinomas are a rare cause of hyperthyroidism, when compared with the more prevalent primary hyperthyroidism, with an overall prevalence of about one in one million. The hormonal profile is characterized by a non-suppressed TSH in the presence of high levels of free thyroid hormones (fT4, fT3).

Failure to recognize a TSH-oma could lead to improper therapy and dramatic consequences for the patient, including an aggressive transformation of the adenoma, visual field defects or hypopituitarism. Most cases correspond to macroadenomas, microadenomas being exceptional. Nowadays, ultrasensitive TSH assays allow better distinction between patients with primary hyper-

thyroidism and those with thyrotropinoma or pituitary resistance hormone.

First-line therapy is surgery, by which about one third of patients can be cured. If this fails, radiotherapy or SSA should be considered.

We present the case of a patient with palpitations and a previously mistaken diagnosis of primary hyperthyroidism. After extensive investigations, this was found to be due to a micro-thyrotropinoma and she was effectively treated with surgery and somatostatin analogs.

CASE REPORT

A 54-year-old woman was referred to our clinic with a two-year history of palpitations. She was on propanolol prescribed by her general practitioner (GP), and she had no relevant family or personal past medical history, apart from an overactive thyroid, diagnosed and treated in Canada when she was 34 years old. Initially she was treated with drugs for 2 years, after that, she was given radioactive iodine with no more follow-up.

She had a high thyrotropin stimulating hormone (TSH) of 12.16 mU/L (normal range 0.35-5.50) and a high fT4 (2.7 ng/dL, normal range 0.9-1.8) when checked by her general practitioner (GP) 12 months ago. Thyroid antibodies were all negative. Despite being on propanolol, she continued symptomatic (feeling hot and with palpitations), so her GP had her thyroid hormone tests repeated, which again showed a markedly elevated fT4 (2.7 ng/dL) and an elevated TSH (9.28 mU/L). With these results, and suspecting a thyrotropinoma or thyroid hormone resistance (RTH), she was referred to the Endocrinology department.

Examination was unremarkable, although she did have a small goiter and tachycardia. In order to really firm up the results, thyroid hormones were repeated in another laboratory showing once more a high TSH with high fT4 and fT3 (Table 1). The sex hormone-binding globulin (SHBG), the TSH alpha subunit (α-SU) (repeated twice) and the α-SU/TSH molar ratio were also elevated (Table 1). The existence of possible interferences between TSH and fT4 was excluded after analyzing these results by equilibrium of dialysis. As the patient was still symptomatic despite treatment with propanolol, she was started on low-dose carbimazole (5 mg, twice a day) to avoid higher TSH stimulation. Further studies were organized, including magnetic resonance imaging (MRI), a thyroid releasing hormone stimulation (TRH) test, a thyroid ultrasound and a thyroid scintigraphy. The MRI showed a pituitary microadenoma expanding into the pituitary fossa with no extension to either the suprasellar cistern or the optic chiasm (Figure 1). The response to the TRH test was flat (Table 2). The ultrasound confirmed the presence of a 2.5 x 2.1 x 1.9 cm solid nodule in the right lobe. The thyroid scintigraphy also showed a right cold nodule and a fine-needle aspiration punction was performed to rule out malignancy.

To further delineate whether the pituitary mass was a thyrotropinoma or an incidentaloma, an octreotide suppression test was performed. As it showed an appropriate suppression after 6 hours (Table 3), transsphenoidal resection of the tumor was planned. To achieve euthyroidism before the surgical resection, a therapy with lanreotide (20 mg per month) was started for three months. Other preoperative investigations included an anterior pituitary screening, showing intact axes (Table 1).

Table 1. Time-course of biochemical determinations

Hormones	Pre-surgery	Post-surgery	6 months post-surgery (on SSA)	4 years post-surgery (on SSA)
TSH (nr: 0.35-5.5 mU/L)	9.28	7.9	3.95	1.66
fT4/fT3 (nr: 0.9-1.8 ng/dL/2.3-4.3 pg/mL)	2.3/7.7	2.1/6.2	1.3/3.2	1.5/3.6
αSU (nr: 0.5-3 µg/L)	4.01/6.45	3.2	nd	nd
SHBG (nr: 30-100 nmol/L)	127	109	nd	nd
αSU (µg/l)/TSH (mU/L) x10 (nr: < 1)	4.3/6.9	4	nd	nd
LH/FSH (nr: > 30 mU/mL)	35/45	33/46	nd	nd
Estradiol (nr: < 30 pg/mL)	33	32	nd	nd
IGF-1 (nr: 105-353 ng/mL)	232	229	nd	nd
ACTH (nr: 10-80 ng/L)	36	31	nd	nd
Cortisol (nr: 6.5-22.5 ng/dL)	22	23	nd	nd
PRL (3-30 ng/mL)	16	19	nd	nd

nr: normal range, nd: not done.

Table 2. Response to the TRH test (after 200 µg of TRH)

	TSH (mU/L) (nr: 0.35-5.5)	fT4 (ng/dL) (nr: 0.9-1.8)
0 min	10.6	3.7
20 min	10.4	3.2
60 min	10.7	3.5

nr (normal baseline range).

Table 3. Octreotide Suppression Test (after 100 µg subcutaneous of Octreotide)

Time	TSH (mU/L) (nr: 0.35-5.5)	fT4 (ng/dL) (nr: 0.9-1.8)
09.30	7.5	3.1
10.30	6.3	2.9
11.30	6.1	2.8
12.30	5.5	2.6
13.30	5.2	2.5
14.30	4.8	2.2
15.30	4.4	1.9

nr (normal baseline range).

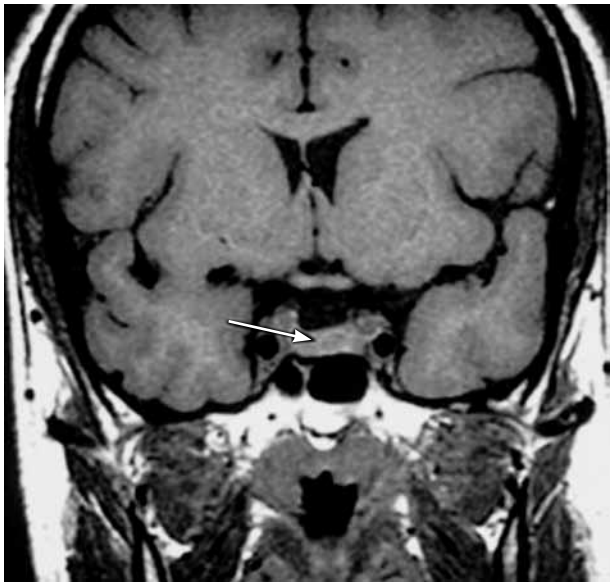

Figure 1. MRI at diagnosis, showing a pituitary microadenoma.

During surgery, complete tumor removal was not possible but a sample of tissue for histological analysis was taken. Histopathology revealed an acidophilic adenoma with strong positive TSH staining, a very low MIB1 (1%) and no p53 overexpression. There were no postoperative complications although she remained on hydrocortisone until her adrenal axis could be reassessed at 6 weeks. Thyroid hormones (obtained one week after the operation) suggested no full effectiveness of the surgery (Table 1), so she continued with lanreotide (20 mg per month). Further treatment options such as radiotherapy were considered. Nowadays, 4 years later, she remains on medical treatment and radiotherapy has been ruled out, as the tumor volume has reduced and she is successfully asymptomatic with TSH levels in the normal range.

DISCUSSION

Thyrotropinomas are rare pituitary adenomas and an even more rare cause of hyperthyroidism. The biochemical features are quite characteristic, as the levels of circulating free thyroid hormones (fT3, fT4) are elevated in the presence of normal or high serum TSH concentrations. The first case of TSH-oma was documented in 1960 by measuring serum TSH levels with a bioassay (1) and since then, approximately 300 cases have been described. With the introduction of ultrasensitive immunometric TSH assays, nowadays it is possible to diagnose TSH-omas earlier, even before the stage of macroadenoma.

Failure to recognize a TSH-oma may result in dramatic consequences such as improper surgery or ablation that may cause the pituitary tumor volume to further expand and become an invasive macroadenoma (2). This could probably be due to similar mechanisms that lead to aggressive transformation of pituitary cells after adrenalectomy in Nelson's syndrome (3).

Molecular mechanisms leading to the formation of thyrotropinomas are currently unknown. Somatic mutations of thyroid hormone receptors, increased expression of basic fibroblast growth factor and loss of heterozygosity, and particular polymorphisms of somatostatin receptor type 5 are thought to be involved in tumor pathogenesis (4-6).

In patients with TSH-oma, signs and symptoms of hyperthyroidism are frequently associated with those related to tumor expansion such as headache and visual field defects (7). Signs of thyrotoxicosis may vary from severe to absent, although clinical features are usually milder than expected for the levels of thyroid hormones. This is probably due to the longstanding duration of the disease. As 30% of thyrotropinomas co-secrete other hormones additional symptoms of hormone hypersecretion are often associated. On physical examination, the presence of goiter is the rule (more than 90% of patients with TSH-oma present with goiter), even in patients with previous thyroidectomy/ablation, as thyroid residue can regrow due to TSH hyperstimu-

lation (8). This was also found in our patient despite her thyroid having been ablated in the past.

When suspecting a TSH-oma, and given its low prevalence, inadequate measurement of TSH and thyroid hormones should always be taken into consideration, and laboratory measurements should be repeated, as it was in our case. This could, for example, occur in medical therapy with amiodarone, in the presence of anti-T4 autoantibodies, in familial dysalbuminemic hyperthyroxinemia and in association with increased levels of hormone-binding globulins (thyroxine binding globulin, albumin or transthyretin) (9). Once this possibility is excluded, it is important to make an appropriate differential diagnosis between a TSH-secreting pituitary adenoma and the syndrome of thyroid hormone resistance (RTH) (10), as in both syndromes, patients present with high peripheral thyroid hormone levels, inappropriately normal or elevated levels of TSH and symptoms of thyrotoxicosis.

TSH, FSH and LH share a common α-subunit (α-SU) that is co-secreted with the pituitary hormones. The measurement of this subunit can be very useful to diagnose thyrotropinomas. Therefore, high levels of α-SU or an α-SU (μg/L)/TSH (mU/L) x 10 > 1 (11) are indicative of thyrotropinoma in more than 90% of the cases (although a normal result does not exclude this diagnosis). In our patient, both α-SU levels and the α-SU/TSH molar ratio were concordant with the existence of a thyrotropinoma. Moreover, other markers of thyroid hormone action, such as the sex hormone-binding globulin (SHBG), can help us with the diagnosis, (specially differentiating thyrotropinomas from thyroid hormone resistance), as they are known to be elevated in 80% of TSH-omas.

Regarding dynamic tests, both stimulatory and inhibitory tests have been proposed for the diagnosis of thyrotropinomas. Classically, the T3 suppression test (80-100 μg of T3 per day for 8-10 days) has been used to assess the presence of a thyrotropinoma. This test is specially sensitive and specific when studying a patient with previous thyroid ablation or differentiating TSH-omas from secondary pituitary hyperplasia (8). Although a complete inhibition of TSH secretion after this test has never been recorded in patients with a thyrotropinoma, it is contraindicated in elderly patients or those with coronary heart disease. Therefore, the TRH test has also been widely used, although it is less sensitive in patients with prior thyroid ablation. In the vast majority of patients with thyrotropinoma, TSH and α-SU levels do not increase (or increase less than 2-fold) after TRH administration, in our case TSH did not increase at all. Moreover, in patients with hyperthyroidism, discrepancies between TSH and α-SU responses to TRH are pathognomonic of TSH-omas co-secreting other pituitary hormones.

To complete the diagnosis, and in suspecting a TSH-oma, a MRI is very useful, and it is nowadays the preferred tool for visualization of a thyrotropinoma. However, pituitary tumors on MRIs have to be interpreted carefully, as pituitary incidentalomas can be found in up to 10% of the population (12). In most cases (80%) (13), as previously stated, a macroadenoma is found, although due to the ultrasensitive TSH assays microadenomas are now increasingly reported (10%-20%) (14).

In our patient, given all the results (elevated α-SU concentrations, high α-SU/TSH molar ratio, TSH unresponsiveness to TRH stimulation, microadenoma in the MRI) and the absence of biochemical data in other family members, the diagnosis of thyrotropinoma was favored, and the possibility of a RTH was ruled out.

Once diagnosis of TSH-oma is made, removal of the tumor and restoration of euthyroidism are the primary goals of treatment. Therefore, the first therapeutic approach should be the transsphenoidal/subfrontal adenomectomy, as this is the only recourse which can lead to cure. However, complete resection of the tumor is not always possible, as it often presents marked fibrosis or may be locally invasive involving the cavernous sinus, carotid artery or optic chiasm. So, only 40% of patients who undergo surgery are completely cured (15). Prior surgery, antithyroid drugs or octreotide along with propanolol can be administered in order to achieve euthyroidism (16). It is worthy of note that antithyroid drugs should only be used in this situation and not as a chronic treatment, as they can cause fast and invasive growth of these tumors. If surgery is contraindicated or declined, pituitary radiotherapy should be considered although even after surgery and pituitary irradiation, additional medical treatment is sometimes needed. Dopamine agonist therapy and SSA are the drugs used for this aim. The presence of dopamine receptors in thyrotropinomas was the rationale for its use. Several studies have shown heterogeneity in TSH responses to these agents and the best results have been achieved in mixed TSH/PRL adenomas (17). However, in the current literature, the efficacy of dopamine agonists is controversial, and its use has decreased in favor of SSA (18), which have

become the drug of choice. This is because, nowadays, it is known that most thyrotropinomas (90%) show sensitivity to native somatostatin and its analogs. Indeed, they can be useful helping either in the differential diagnosis of problematic cases of central hyperthyroidisms (when administered for at least 2 months prior to surgery) or as long-term treatment (added to surgery or radiotherapy) (19). This way, they can revert thyroid hormone levels in about three quarters of the patients and make the tumor shrink in one third of the patients.

Regarding medical treatment, it is important to keep thyroid hormone levels at upper limits of normal to prevent an additional stimulus of the pituitary tumor to expand (20).

In conclusion, TSH-omas are rare adenomas. Diagnosis may often be delayed because the symptoms are attributed to more common causes of thyrotoxicosis. This delay and misdiagnosis, coupled with the usually aggressive nature of these tumors, allows them to become large and invasive. The primary goal in treatment must be surgical adenomectomy, and when it is not successful radiotherapy or medical treatment should be added. Our case is specially interesting, given the low prevalence of this pathology, its diagnosis at the stage of microadenoma (despite prior thyroid ablation and the delay in the diagnosis) and its successful long term medical treatment with SSA, with no need of further radiotherapy.

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