
TRABAJO ORIGINAL

Long-Term Follow Up of Thyrotropinomas: The Role of Radiotherapy and Long-Acting Somatostatin Analogs. Report of Two Cases

Evolución a largo plazo de tirotropinomas: papel de la radioterapia y análogos de somatostatina de acción prolongada. Reporte de dos casos

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ABSTRACT

Thyrotropinomas or TSHomas are functioning pituitary adenomas that produce central hyperthyroidism and are often detected at macroadenoma stage, with the expected mass effects of large pituitary tumors. We report the long-term outcome of two thyrotropinomas, and discuss the treatment options adopted and available for these patients. Our first patient was seen 4 years after diagnosis of hyperthyroidism and two years after pituitary surgery, with persistent disease. The second subject was diagnosed soon after the detection of a symptomatic pituitary mass with extrasellar extension, with the corresponding clinical and laboratory workup. None of them was cured by surgery alone; both were treated with somatostatin analogs and radiotherapy with a clear improvement of their condition. **Rev Argent Endocrinol Metab 52:120-128, 2015**

No financial conflicts of interest exist.

Key words: Thyrotropinomas. Long-term evolution. Radiotherapy, octeotride

RESUMEN

Los tirotropinomas son raros adenomas hipofisarios funcionantes, que producen hipertiroidismo central y, como se suelen detectar en el estadio de macroadenomas, con los signos de masa correspondientes. Presentamos la evolución a largo plazo de dos tirotropinomas para analizar las opciones terapéuticas adoptadas y disponibles para estos pacientes. Nuestro primer caso fue visto 4 años después del diagnóstico de hipertiroidismo, y dos años pos cirugía pituitaria, con enfermedad persistente. El segundo sujeto fue diagnosticado poco después de la detección de una masa hipofisaria, con expansión extraselar sintomática, mediante la evaluación clínico endocrinológica y de laboratorio pertinente. Ninguno de los dos fue curado por la cirugía solamente; ambos fueron tratados con análogos de somatostatina y radioterapia, con un claro beneficio clínico, imagenológico y bioquímico. **Rev Argent Endocrinol Metab 52:120-128, 2015**

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Palabras clave: Tirotropinomas. Evolución alejada; radioterapia; octeotride

INTRODUCTION

Thyrotropinomas or TSHomas, are rare pituitary neoplasms⁽¹⁾, that comprise less than 2 % of all

hypophyseal tumors. They are usually detected at the stage of macroadenomas. These pituitary tumors⁽²⁾ produce central hyperthyroidism and the corresponding local manifestations of the mass.

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Even nowadays around 30 % of patients are treated previously as if they have had different forms of hyperthyroidism of thyroideal origin⁽³⁾, which can turn their management difficult and worsen the natural course of the disease.

MATERIAL AND METHODS

The medical records of 2 patients with a diagnosis of thyrotropinoma were exhaustively reviewed with emphasis in clinical presentation, laboratory and imaging results, according to treatments employed at different periods of the evolution. The trend over time in TSH values was analysed by an ANOVA test.

RESULTS

Case 1

A 73 years old caucasian asymptomatic woman consulted because of a pituitary tumor that had been operated two years before. At age 69 a diagnosis of overt hyperthyroidism was made [T4: 19.5 ug/dl (nv: 4.5-12.5 ug/dl)] with an elevated TSH [5.63 uU/ml (nv: 0.27-4.20 uU/ml)]. Months before, she had had atrial fibrillation, along with a 10 % decrease in body weight, without headaches or ocular complaints. A 5 mCi dose of I¹³¹ had been

given that resulted in hypothyroidism, so she had been placed under levothyroxine (LT4) (100 ug/day). At age 71, because a progressive increase in TSH [maximum: 33.10 uU/ml, (Table 1, period A)], in spite of normal serum T4 (Table 2,A), a pituitary MRI was performed, that depicted a macro adenoma of 2.8 cm height, with upward displacement of the pituitary stalk and chiasm, and bilateral contact with the cavernous sinuses (Figure 1, A). Serum PRL was slightly elevated, IGF1 normal, and serum cortisol decreased. Hydrocortisone (30 mg/day) was added to levothyroxine. A surgical transphenoidal pituitary approach of the tumor was done, partially resecting an adenoma that stained positive for TSH. The procedure reduced the cephalocaudal length of the tumor to 2,2 cm (Figure 1, B). After surgery, a drop of serum TSH to 4,15 uU/ml was noted, followed by a stepwise increase up to 20.43 uU/ml [(Table 1, period B), with normal T4 (Table 2, B), during the next 20 months. At this moment she was seen by us for the first time. Physical examination showed a kyphotic woman, 1.56 mts height, with a body weight of 64 kg (BMI: 26.30KG/M2), blood pressure 150/80 mmg/Hg, pulse rate 80 beats/min. Laboratory workup was as follows: T4: 10.7 ug/dl, free T4: 1.25 ng/dl (nv: 0.94-1.7 ng/dl), T3: 63 ng/ml (nv: 79-149) and TSH: 20.43 uU/ml (0.35-4.69). Hypopituitarism was diagnosed because of low levels of IGF1 [50 ng/ml (n:

TABLE 1. Case #1: TSH evolution after 7.9 years of follow up(n being the number of observations during each period) [(ANOVA: F: 8.88; p < 0.0003). *POST-HOC ANALYSIS: P < 0.05

CASE #1: TSH EVOLUTION OVER TIME				
Period (months)	n	TSH (uU/ml; n: 0.35-4.69)	SD	Range
A (21): after RAI	5	22.63*	6.10	17.25-33.10
B (20): post Sx: TSSPA	4	12.09	7.08	4.15-20.43
C (12): SSA	4	14.17	2.69	12.00-17.89
D (24): Radiotherapy add on	6	11.21	2.12	7.80-13.38
E (18): idem D	6	7.93	1.90	5.20-10.96

TABLE 2. Case #1: T4 evolution after 7.9 years of follow up (n being the number of observations during each period)

CASE 1: Total T4 (4.5-12.5 ug/dl)			
Period	Mean	SD	Range
A(18 mths), n:5	9.3	0.9	8.3-11.4
B(21 mths) n:4	8.7	0.9	7.9-10.5
C(9mths) N:4	9.25	0.6	8.7-10
D(21mths) n:6	8.4	0.4	7.9-8.9
E(42mths) N:6	7.91	0.4	7.4-8.4

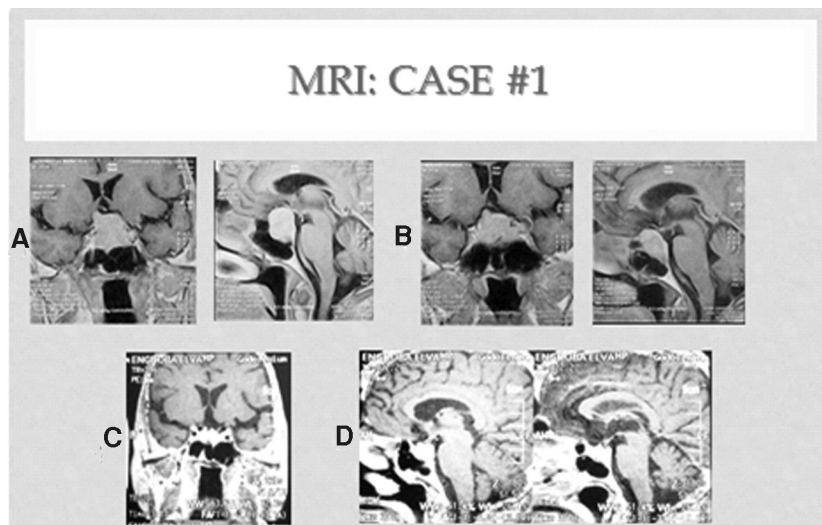


Figure 1. Case #1 A: Left upper panel: before surgery. **B: right upper:** postTSSPA. **C:** left lower panel: 1 y after radiotherapy plus octeotride. **D:** lower right panel; at the end of follow up(3.5 ys after radiotherapy).

70-350]), FSH (2.8 mU/ml) and ACTH (5.8 pg/ml). Alkaline phosphatase was high. The patient was menopausal since age 49 and had experienced a lateral neck fracture at age 66. She was aware of having had a lumbar crush fracture.

Lumbar spine and femur neck BMD were reduced with a - 4.07 and -5.46 TS, respectively. Rx examination of the spine showed the known

L1 crush and 2 incident fractures, at T9 and T12 levels. She had established osteoporosis.

A long acting somatostatin analogue (SSA), octeotride, was offered to her and escalated up to 30 mg IM/month. In addition, risedronate 35 mg/week and ergocalciferol 2400 IU/week were initiated while hydrocortisone was reduced to 20 mg/day, and thyroid hormone switched to a fixe combination

of T3(10 ug/d) and L T4 (90 ug/d). TSH remained elevated (although less fluctuating) [(Table 1, period C), (max v: of 17 uU/ml)] [and Table 2, C), by this approach, without significant changes in tumor size. One year later, radiotherapy of the pituitary was instituted, receiving 50 Gy after threedimensional virtual planning. Octeotide was maintained. During the next 2 years (Table 1, period D) TSH was slightly reduced, with a stable mean T4 (Table 2, D). Three and a half years after radiotherapy plus SSA, the mean TSH value was 7.93 uU/ml, 1 (Table 1, period E) & (Table 2, E). The MRIs performed one year and 3.5 years after radiotherapy was given (Figure 1: C&D) showed a progressive decrease in the adenohypophyseal volume, accompanied by an increase in the width between the upper edge of the gland and the chiasm, so at the end of the 8 years of follow up, the height of the pituitary was 1 cm.

Overall, a sustained tendency towards lower TSH levels was obtained by the successive and additive treatments during an almost 8 years of follow up.

A rapid normalization of alkaline phosphatase was noted and bone mineral density (BMD) improved markedly at LS and FN (TS: - 3.3, at both sites), by 2 years after the implemented treatment.

The overall clinical evolution was good, the patient being asymptomatic, with a normalization of body weight and BP and a very good quality of life.

Case 2

A 25 years old man had had recent onset frontal headaches, accompanied by occasional diarrhea, heat intolerance, axilar discomfort, and fatigue. An MRI of the brain detected a pituitary macroadenoma with suprasellar extension and posterior displacement of the optic chiasm (Figure 2, A.)

Computerized visual field assessment was normal.

He was referred for endocrinological evaluation, prior to eventual surgery. At physical examination, he was overweight (BMI: 29,7 kg/m²), heart rate was 120 beats/min, regular, and blood pressure 140/80 mmHg. Neither goiter nor ocular or skin abnormalities were evident, but bilateral tender gynecomastia was noticed.

Initial laboratory values were as follows: Free T4: 2.48 ng/dl(nv: 0.93-1.7); total T3: 268 (80-200) ng/ml; and TSH: 6.19 uU/ml (nv: 0.27-4.2 uU/7ml). Prolactin: 43.2 ng/ml (2-15), LH 1.5 mU/ml (nv: 2-9 mU/ml), Total To: 0.35 ng/ml (nv: 2.8-9) and Alkaline phosphatase (AP): 383 UI (nv: up to 280 IU). Basal and (ACTH) stimulated cortisol, ACTH, GH and FSH were within normal values.

Ten months earlier laboratory analysis had been performed, showing an increased TSH (5.18 uU/ml; nv: 0.27-4.2). Alkaline phosphatase was also high. However, no further tests had been ordered at that time by the intervening physician.

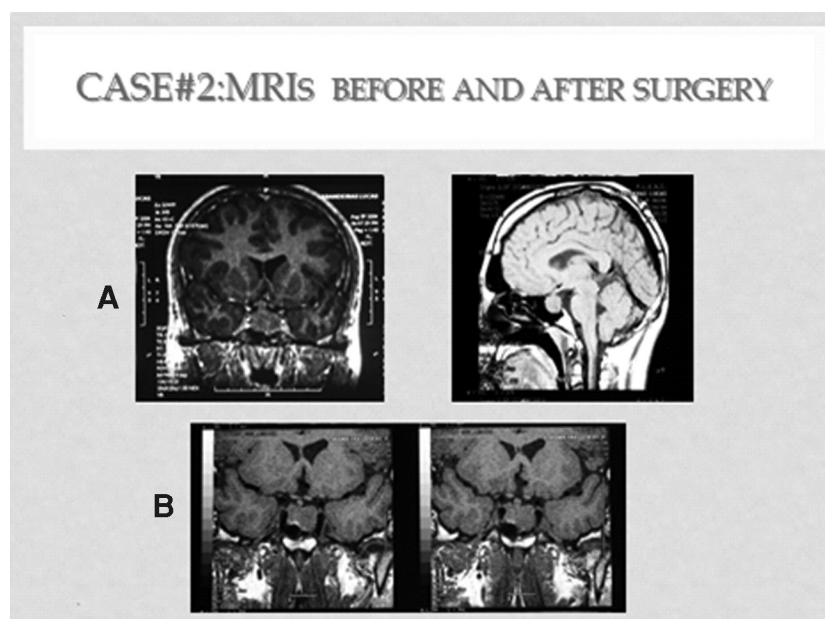


Figure 2. MRIs case #2. A: upper panel: before surgery. B: after TSSPA

Since measurement of alpha subunit was not available, a TRH-TSH test was done. Basal TSH was 6.75 uU/ml and stimulated: 6.86. A diagnosis of TSH secreting pituitary adenoma was made, without concomitant secretion of GH, ACTH or gonadotrophins, accompanied with hypogonadotropic hypogonadism and hyperprolactinemia, either secondary to stalk distortion or cosecretion by the tumor.

Prior to transsphenoidal pituitary microsurgery, the SSA octeotide was prescribed at an initial dose of 20 mg IM, followed by a second 30 mg dose, a month later. Clinical resolution of the thyrotoxicosis was obtained, with FT4 of 1.13 ng/dl, total T3 of 127 ng/ml, and TSH of 1.39 uU/ml.

An uneventful transsphenoidal surgical procedure was done, partially removing fragments of a pituitary chromophobe adenoma, with negative immunostaining for TSH, FSH, LH, GH, ACTH and PRL. Ki 67 was < 1 %. A month later TSH was 0.87 uU/ml, PRL 22 ng/ml, ACTH stimulated cortisol was also normal, as well as T4 and T3. Cabergoline was initiated at 0.25 mg per week, with normalization of serum PRL and amelioration of gynecomastia. SSA therapy was not reinstated.

Post surgery MRI showed a decompression of the chiasm along with central reduction of the adenoma, but significant tumor remnants with lateral contact with the cavernous sinuses, were also apparent (Figure 2,B).

Bone mineral density revealed osteopenia at femoral neck (TS: -1,9) and lumbar spine (TS:-1,4). Testosterone replacement normalized alkaline phosphatase and gynecomastia was resolved.

Mean TSH during the first year post surgery was 1.77 uU/ml (n: 4) (Table 3, B) and FT4 was 1.54 ng/dl (n:4), (Table 4, B) with 2 values slightly above the upper limit of normality. MRI did not change further.

A decision was made, taking into account patient preferences, to perform pituitary radiotherapy, preceded by three-dimensional conformational planning. A total dose of 43 Gy was delivered, one and half years after surgery. During the following two years mean TSH was 3.1 uU/ml (n: 9,) (Table 3,C) and FT4 1.68 ng/ml (n: 7), with 4 out of 7 values above the upper limit of normality (1.7 ng/dl.) (Table 4,C). Basal and stimulated cortisol values were still normal and PRL was 1.1 ng/ml under cabergoline treatment.

Two years after radiotherapy, MRI depicted a superior and central cystic area with significant reduction in overall tumor volume. This was accentuated with time, showing a partial secondary empty sella appearance. At that time, and as a consequence of a trend towards central hyperthyroidism, the SSA was reinstated (30 mg every 45 days). TSH was normalized: 1.15 uU/ml (n:4), but subclinical central *hypothyroidism* resulted. The octeotide

TABLE 3. Case #2. Mean TSH trend over time. A: Before treatment. B: After surgery. C: post radiotherapy. D: SSA add on Tx. E: without medical treatment. ANOVA: F: 21.75; p < 0.0000).(post -hoc test: p < 0.03)

CASE #2MEAN TSH VALUES				
Period (months)	n	TSH (X)(uU/ml; nv: 0.27-4.2)	SD	range
A (s)	4	6.5*	1.13	5.18-7.89
B (4)	4	1.77	0.92	0.87-3.05
C (24)	9	3.27**	0.92	1.78-4.59
D (45)	16	1.24	0.67	0.11-2.33
E (9)	1	1.12		

dose was reduced progressively to 20 mg every 60 days. Although TSH remained normal, central hypothyroidism persisted, so levothyroxine was added with normalization of LT4, Finally, both drugs were interrupted. The duration of SSA treatment lasted 5 years and 5 months, during which mean TSH was: 1.24 uU/ml (Table 3,D), and FT4 was 0.98 ng/dl (Table 4,D). Nine months after treatment ar-

restment, TSH was 1.12 uU7ml and FT4 1.10 ng/dl. (Table 4,E). MRIs of the pituitary showed a progressive increase in the central cystic area of the adenohypophysis, so that at the 8 th year of follow up, a partial empty sella turcica developed, thus revealing an important reduction in the overall volume of the adenoma, without appreciable long term sequelae of radiotherapy. (Figure 3).

TABLE 4. Case #2. Free T4 trendover time. Anova F: 8.94,p<0.0001

CASE 2: FT4(0.93-1.7ng/dl)

Period	FT4	SD	Treatment
A(6mths) n:2	2.21	0.38	Before
B(6mths) n:4	1.54	0.33	Post-surgery
C (24 mths) N:9	1.68	0.20	Post radiotherapy
D(65mths) N:16	0.98	0.30	SSA add on
E(9mths) N:1	1.1	—	None

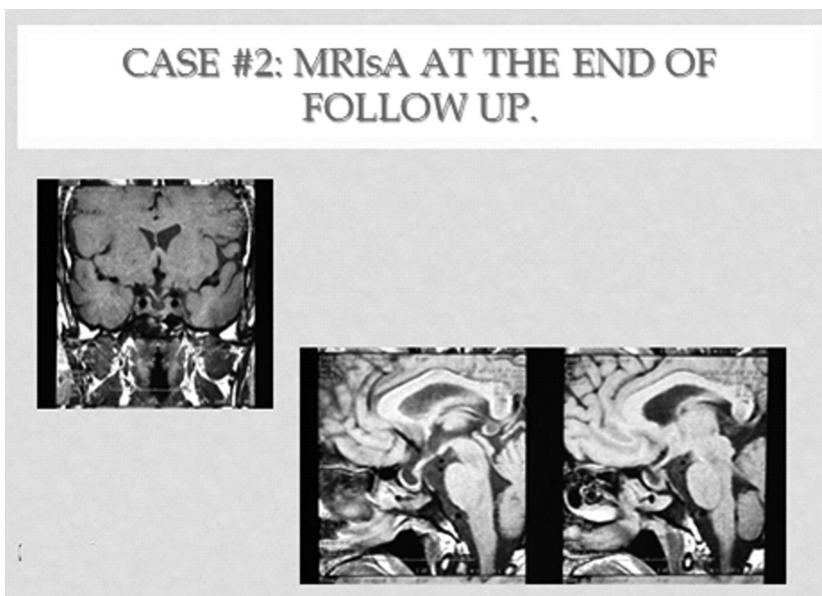


Figure 3: MRIs case #2: at the end of the observation period: 9.1 ys.

During time, laparoscopic cholecystectomy was performed, secondary adrenal failure appeared, IGF 1 still remained normal and femoral neck and lumbar spine BMD were normalized (TS: -0.6 and 0.2, respectively).

DISCUSSION

Thyrotropinomas are frequently located centrally within the adenohypophysis. They are usually sporadic and fibrous, probably⁽⁴⁾ as a consequence of basic fibroblast growth factor (FGF) expression. The pathophysiology of TSHomas is unknown; however overexpression of Pit-1 factor⁽⁵⁾, perhaps in combination with mutations of⁽⁶⁾, may contribute to their development. A very recent series⁽⁷⁾ of 5 patients, was published in Argentina. Most of them were followed for less than five years, with the exception of 1 subject with an observation period of 8 years. Unfortunately, the patient with the worse prognosis was lost from follow up soon after diagnosis. Nonetheless, 3 patients, with tumor's diameter ≤ 3.0 cm were cured. No subject had been previously treated with either thyroidectomy or I¹³¹.

Thus we have presented two cases followed for 8 and 9 years, respectively, aiming to contribute to the regional experience with these rare pituitary tumors.

Our first case is representative of those patients in whom a misdiagnosis of primary hyperthyroidism (probably Graves' disease) resulted in radioiodine treatment followed by post dose hypothyroidism, two years before surgery. Her hyperthyroidism was moderate to severe and evidence of ACTH deficiency was already evident previous to TSSPA, attributable to the mass effect of a large macroadenoma with suprasellar extension. In the Belgium-French series published by Socin et al⁽⁸⁾, 13 out of 43 patients (30 %) had received a treatment targeted to the thyroid before pituitary surgery. Patients previously treated with radioiodine or thyroidectomy, are detected with greater delay from the initial symptoms of hyperthyroidism^(2,9), present more frequently macroadenomas with compression signs, higher TSH levels, and experience a worse prognosis⁽⁸⁾, most probably as a consequence of insufficient negative feedback of thyroid hormones with the tumor⁽⁶⁾ allowing it to grow further during longer periods of time; however, this conclusion⁽⁸⁾, is not proven. Our first case suggests that this might be correct, as

it happens in Nelson's syndrome. Socin⁸ et al did not find greater tumor volumes in patients that had been previously treated with thyroidectomy or I¹³¹. However, adenomas' diameter⁽⁸⁾ was higher in patients treated with TT or RAI than in those that received methimazole. After Drucker Davis et al⁽⁹⁾, severity of hyperthyroidism, duration of symptoms and tumor size and invasiveness were the main prognostic factors.

The suspicion of a TSHoma is likely⁽⁹⁾ in a patient with thyrotoxicosis, elevated free T4 and T3, without biochemical confounders, in whom sensitive TSH is slightly elevated or even inappropriately normal, distinguishing him from primary hyperthyroidism. TSH^(2,6,7,9) is frequently between 4 and 14 μ U/ml. The biochemical gold standard for diagnosis⁽⁸⁾ is still the measurement of α subunit in the appropriate context, which is overexpressed in TSHomas, resulting in an absolute increase with an elevated molar ratio of α subunit/TSH. The most important distinction is between tumoral and non tumoral inappropriate TSH secretion⁽¹⁰⁾ namely thyroid hormone resistance syndromes (THR). We could not measure α subunit in neither patient, but in case #2 we were able to demonstrate the lack of response to TRH, that can differentiate TSHomas from the normal response seen in THR⁽¹⁰⁾. In 3 out of 5 patients reported in Argentina⁽⁷⁾ TRH-TSH test was also flat. Our two patients had either osteoporosis (case 1) or osteopenia (case 2). In addition, both had high alkaline phosphatase. The two cases were hypogonadal, as the female patient was menopausal, and the male one had secondary hypogonadism from the diagnosis. It should be stressed that the combination of thyrotoxicosis with hypogonadism is particularly dangerous for the skeleton. We thus suggest that bone status and/or remodeling needs to be evaluated in patients with TSHomas, especially when there is a compromise in the gonadal axis.

As with other functional pituitary adenoma^(1,8,9,11), with the exception of prolactinomas, surgery is the treatment of choice. In thyrotropinomas^(8,11,12) its effectiveness is inversely related with tumor size, success being greater in microadenomas. The overall success rate seems to be around 60 %. It is generally accepted that cure should include a persistent normalization of the thyroid axis dynamics, as well as the absence of residual tumor demonstrated by MRI. Our two patients had residual disease after surgery, so they were not

cured by the procedure. Nonetheless, a decompression of the optic chiasm was achieved, along with a temporal but significant reduction in TSH. In accordance with patients' preferences, we did not re-operate them. Radiotherapy, which is a second line treatment, was offered instead. Prevention of tumor growth and its consequences was the therapeutic priority in both. In case 2, although he could have been further treated by medical means, the patient's fear of tumor expansion contributed to our decision of irradiating the adenoma relatively early in the course of the disease. This procedure was well tolerated, without side effects and, in the long run, helped both of them to control their condition. In addition, a reduction in tumor volume was evident in both cases. Moreover, although not cured, our 2nd patient finally achieved a remission of his hyperthyroidism and tumor growth, the latter most probably as a consequence of radiotherapy without ancillary medical treatment. And our first patient remained euthyroid, albeit substituted, as a result of radiotherapy plus medical treatment, with a clear reduction of her tumor volume. TSHomas usually express somatostatin receptors. Accordingly^(8,13), somatostatin analogs have been used for the treatment of TSHomas. As we did with our second patient, they are primarily indicated for the preoperative treatment of hyperthyroidism. Thyronamides are only a second option for the preoperative medical treatment of hyperthyroidism. SSA can be employed as second, or third line treatment alternatives. They were assayed in our first patient, when first seen, after failure of surgery to remove the adenoma and uncontrolled TSH values. Octeotide alone was unable to reduce tumor size, but there was an amelioration of the visual field. TSH was slightly diminished, although not normalized. Consequently radiotherapy was implemented. The combination of both permitted a better control of hypersecretion of TSH, but the shrinkage of the tumor seems to be primarily a result of radiotherapy. Our male patient responded very well to octeotide for the treatment of hyperthyroidism. The drug could have been employed as a second line option, after the failure of surgery as a curative treatment. As aforementioned, patient's preferences prompted us to irradiate the macroadenoma instead. It was only after the reappearance of subclinical central hyperthyroidism that octeotide was reinstated, with an excellent although excessive response that allowed us to

stopped it. Development of central hypothyroidism⁽¹⁴⁾ in a girl with a thyrotropinoma treated with a SSA alone, has already been reported.

CONCLUSIONS

We report the long term evolution of two patients with thyrotropinomas after failure of transsphenoidal pituitary surgery to resolve their condition. Our first case is representative of a clinical situation that should no longer be seen: a misdiagnosis of primary hyperthyroidism in the context of inappropriate secretion of TSH. Her disease could be managed with a combination of radiotherapy plus octeotide. Our second subject was treated from diagnosis with an effective combination of a SSA, prior to surgery, plus the subsequent addition of radiotherapy.

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REFERENCES

1. **Oruckaptan HH, Sanmevsin O, Ozcan OE, Ozgen T, Gesundheit N, Petrick PA, Nissim M, Dahlberg PA, Doppman JL, Emerson CH, Braverman LE, Oldfield EH, Weintraub BD** Pituitary adenomas: results of 684 surgically treated patients and review of literature. *Surg Neurol*, 53:211-219, 2000
2. **Gesundheit N, Petrick PA, Nissim M, Dahlberg PA, Doppman JL, Emerson CH, Braverman LE, Oldfield EH, Weintraub BD**. Thyrotropin-secreting pituitary adenomas: clinical and biochemical heterogeneity. Case reports and follow-up of nine patients. *Ann Intern Med*. Nov 15,111(10):827-3, 1989
3. **Kienitz T, Quinkler M, Strasburger CJ, Ventz M**. Long-term management in five cases of TSH-secreting pituitary adenomas: a single center study and review of the literature. *Eur J Endocrinol*, Jul157(1):39-46, 2007
4. **Ezzat S, Horvath E, Kovacs K, Smyth HS, Singer W, Asa**. Basic fibroblast growth factor expression by two prolactin and thyrotropin-producing pituitary adenomas. *Endocr Pathol*,6:125-3,1995
5. **Poncín J, Stevenaert A, Beckers**. Somatic MEN-1 gene mutation does not contribute significantly to sporadic pituitary tumorigenesis. *Eur J Endocrinol*,140:576-576, 1999
6. **Ando S, Sarlis NJ, Oldfield EH, Yen PM** Somatic mutation of TRbeta can cause a defect in negative regulation of TSH in a TSH-secreting pituitary tumor *J Clin Endocrinol Metab*, 86:5572-6, 2001
7. **Pignatta A, Danilowicz K, Manavela M, Loto M, Gonzalez Abbati S, Toloza C, Fazio L**.

- Adenoma hipofisario productor de TSH (tirotropinoma): presentación de cinco casos. *Rev Argent Endocrinol Metab*, 51: 141-150, 2014
8. **Socin HV, Chanson P, Delemer B, Tabarin A, Rohmer V, Mockel J, Stevenaert A, Beckers A.** The changing spectrum of TSH-secreting pituitary adenomas: diagnosis and management in 43 patients. *Eur J Endocrinol*, 148: 433-42, 2003
 9. **Drucker Davis F, Olfield E, Skarulis M, Doppmann JL, WeintraUB BD.** Thyrotropin-secreting pituitary tumors: diagnostic criteria, thyroid hormone sensitivity, and treatment outcome in 25 patients followed at the National Institutes of Health. *J Clin Endocrinol Metabol*, 84(2):476-486, 1999
 10. **Mahler GA, Bergoglio LM.** Inappropriate Secretion of TSH syndrome. *Rev Argent Endocrinol Metab* ;5: 253-264, 2013
 11. **Beck-PeccozP, Persani L,** Thyrotropinomas, *Endocrinol Met Clin N Am* 37: 773-779, 2008
 12. **Losa M, Giovanelli M, Persani L, Mortini P, Faglia G, Beck-Peccoz P.** Criteria of crure and follow up of central hyperthyroidism due to thyrotropin secreting pituitary adenomas. *J Clin Endocrin Metabol*; 81: 3084-90, 1996
 13. **KhunJM, Arlot S, Lfebvre H, Caron P, Corlet-Rudelli C, Archabaud F.** Evaluation of the treatment of thyrotropin- secreting pituitary adenomas with a slow release formulation of somatostatin lanreotide. *J Clin Endocr Metabol*, 85:1487-91, 2000
 14. **Rabbiosi S, Peroni E, Tronconi GM, Chiumello G, Losa M, Weber G.** Thyrotropin –secreting pituitary macroadenoma in a 13 years old girl: successfull first line treatment with a somatostatin analog. *Thyroid*, Oct22(10):1076-1079, 2012