

Research Article

## TSH and GH Producing Macroadenoma. Escape to Control with Long-Acting Somatostatin Analogues (SSA) After 12 Years Follow-Up. About A Case

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### Abstract

Tyroid-stimulating hormone (TSH) - producing pituitary adenomas known as thyrotropinomas or TSHomas account for a small percentage of pituitary tumors [1]. Approximately 30% of them co-secrete growth hormone (GH), Prolactin, or  $\alpha$ GSU of TSH [2]. We introduce a

patient with a 12 years follow-up at our center with medical treatment by long-acting somatostatin analogues (SSA) due to rejected surgery. Along the treatment there is a scape with a secondary production of GH without image changes at the MRIs. We suggest a progressively acquired resistance to the medical treatment.

**Keywords:** Macroadenoma; TSH; GH; Somatostatin analogues; Escape control

## 1. Introduction

Thyroid-stimulating hormone (TSH) - producing pituitary adenomas known as thyrotropinomas or TSHomas account for a small percentage of pituitary tumors [1]. Approximately 30% of them co-secrete growth hormone (GH), Prolactin, or  $\alpha$ GSU of TSH [2]. According to the Swedish national registry of TSH-producing tumors, its incidence has increased to 2.8 cases per million inhabitants [3]. The diagnosis of these tumors can be complex and their analytical manifestations may be confused with a resistance to thyroid hormones. They usually present with signs and symptoms generated by hyperthyroidism together with goiter [2] and symptoms due to the mass effect of the tumor. Although most are macroadenomas at diagnosis, it seems that the better sensitivity of current laboratory and imaging tests could have improved their early diagnosis[4].

Regarding treatment, the guidelines of the European Thyroid Association recommend surgery as the first step in the management of these tumors. Medical treatment consists of the use of long-acting somatostatin analogues (SSA) together with the possibility of using dopamine agonists [5].

We present the case of a TSHoma with 12 years of follow-up at our center.

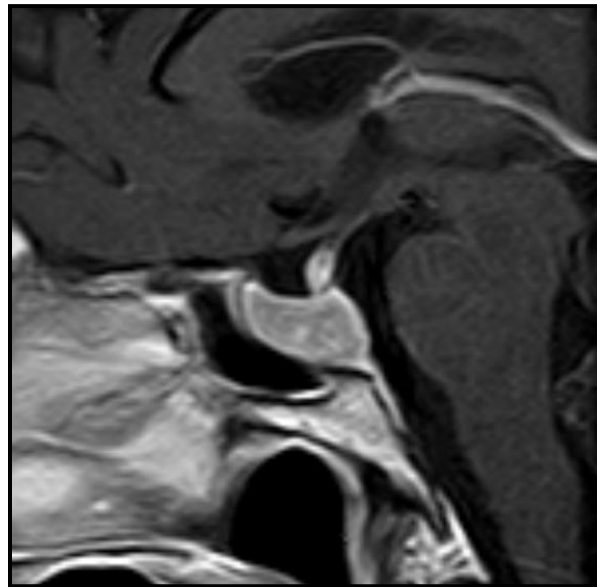
## 2. Case Report

This is a male patient referred to our consultation in 2008 at the age of 73 years. The main reason was the loss of 8 kg of weight and palpitations together with the analytical appearance of TSH of 13.5 mIU / L (0.35-4.94) and T4L in the normal range (0.7-1, 5). Initially, treatment was started with Levothyroxine 25 mcg, which was increased up to 175 mcg daily. As a consequence, TSH remained elevated with T4L, which reached a value of 3 ng / dL. The patient started with a weight of 65 kg which dropped to 58 kg before consultation.

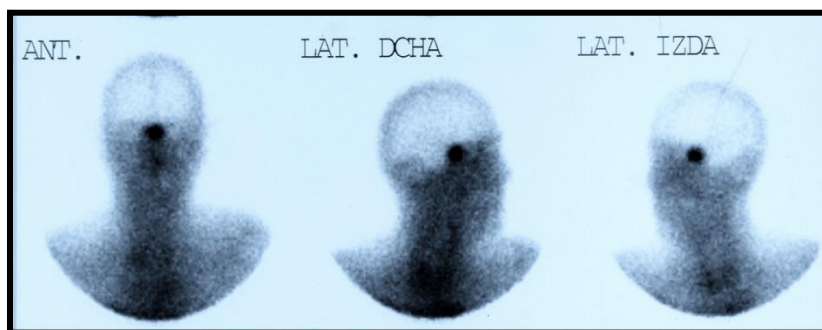
In the absence of analytical control, a TRH test and a SHBG value were requested, showing a basal TSH value of 26.3 and a stimulated value of 26.4 mUI/L. The SHBG value was 120 nmol/L. Because of them, a magnetic resonance imaging (MRI) of the Turkish chair was requested, showing the presence of a pituitary macroadenoma of 25 × 19 × 16 mm (LAT, CC and AP) with infiltration of the left cavernous sinus and walls of the right cavernous sinus contacting the optic chiasm without displacing it (Figure 1 and 2). To complete the study, an Octreoscan (Figure 3) was performed, which was positive for somatostatin receptors.



**Figure 1:** MRI 2008. T1 sequence in sagittal orientation with presence of pituitary macroadenoma  $25 \times 19 \times 16$  mm (volume 3.9748 cc) that infiltrates the left cavernous sinus.



**Figure 2:** 2015 MRI. T1-weighted sagittal image with c.i.v.:  $18 \times 10 \times 18$  mm intrasellar mass (volume = 1.69452 cc).



**Figure 3:** Octreoscan 2009: positive uptake in the pituitary region.

After confirming the clinical diagnosis of TSH-producing macroadenoma (TSHoma), treatment with Octreotide LAR 20 mg was started every 28 days in 2009 with good tolerance and rapid analytical normalization and disappearance of the symptoms described, including the gain of 10 kg of weight. The 2009 MRI control showed radiological stability, so it was decided to increase the dose to 30 mg per day with a 50.3% volume reduction observed the following year. Neurosurgery evaluation was requested,

but given the good clinical and radiological evolution, we agreed with the patient on follow-up and medical treatment. The patient has been following up at our center since then. Table 1 shows the evolution of laboratory values over the years. As seen in the subsequent MRI controls, the size of the adenoma decreases discreetly over time (Table 2). In 2016 an increase in size is reported, which is why we requested two controls in 2017 showing smaller sizes. Since then stability or discreet growth of the lesion has been observed.

Value/Date (M/Y)	2009	12/10	03/11	09/12	09/13	3/14	04/15	08/16	09/17	05/18	06/19	02/20
TSH	10	2,98	3,24	3,1	4,25	2,28	3,76	2,78	2,89	2,58	3,05	2,55
Free-T4		1,6	1,3	1,1	1,2	1,3	1,2	1,2	1,2	1	1	1
Prolactin	12	-	10,5	-	11,5	-	11,8	-	-	6,9	<0,8	<0,8
GH	3,1	-	0,7	-	-	-	1,38	1,97	-	1,06	3,35	2,45
IGF-1	175	-	204	251	272	263	285	300	296	357	301	258
SDS IGF-1	1,16	-	1,84	2,65	3,08	3,1	3,49	3,77	3,78	4,53	3,84	3,25

**Table 1:** Evolution of analytical values during follow-up.

Date (M/Y)	Size in mm (TR/CC/AP) on reports	Volume (cc)
2008	25 × 19 × 16	39,748
2009	25 × 19 × 16	39,748
2010	21 × 12 × 15	19,769
01/2012	22 × 13 × 19	28,419
05/2014	21 × 9 × 19	18,780
05/2015	18x 10 × 18	16,945
04/2016	25 × 13 × 21	35,694
03/2017	19 × 11 × 21	22,954
09/2017	20 × 11 × 15	17,259
06/2018	19 × 13 × 21	27,128
04/2019	19,8 × 12,9 × 20	26,716

**Table 2:** Evolution of adenoma size on MRI. Volume calculated with the formula TRxCCxAPx0,523 (synthesized ellipsoid volume formula).

Time	Glucose (mg/dL)	GH (µg/L)
-15 min	128	1,96
Basal	128	1,98
30 min	166	1,51
60 min	275	1,49
90 min	302	1,37
120 min	332	1,14

**Table 3:** Oral glucose overload test.

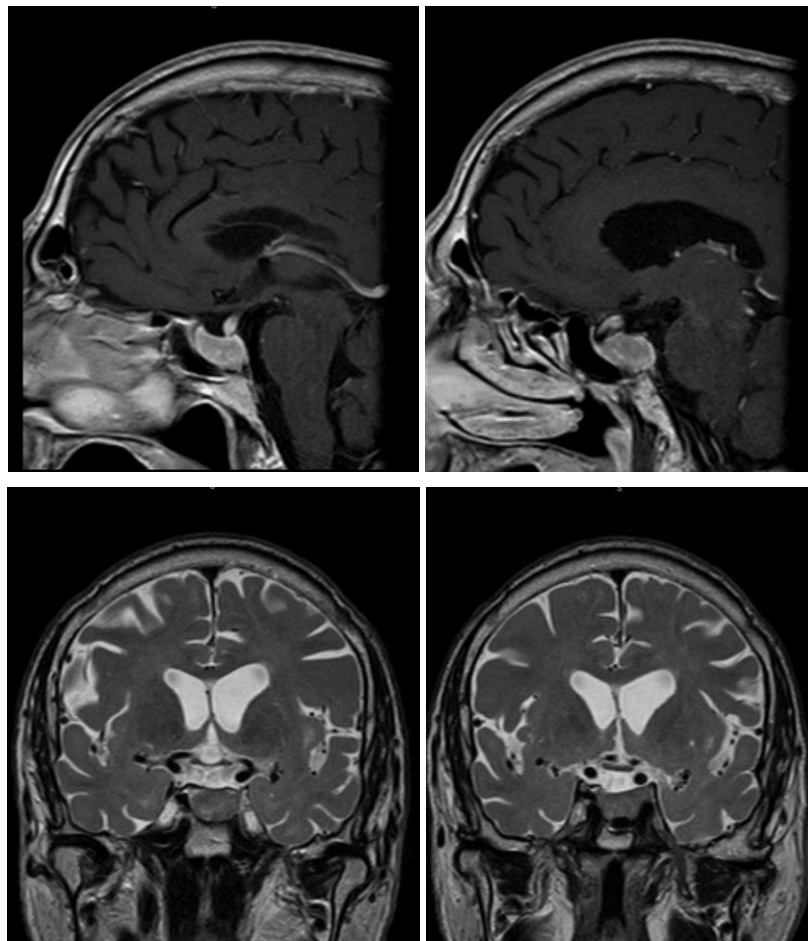
During follow-up, a progressive increase in the IGF-1 value was identified reaching +4.53 SD in 2018. However, the patient did not present acral enlargement or any symptoms related with acromegaly. A GH test was requested after oral glucose overload (Table 3), which was pathological, confirming the co-secretion of TSH and GH. At this time we decided to associate Cabergoline at an ascendant dose of 2 mg per week, achieving a progressive decrease in IGF-1

levels in subsequent controls. Simultaneously, screening tests were requested with the finding of a subcentimetric multinodular goiter, 2 subcentimetric polyps at colonoscopy and a benign prostatic hyperplasia. The patient was also diagnosed with diabetes mellitus, which was kept under control with Metformin 850 mg 1 tablet daily and asymptomatic cholelithiasis. An echocardiogram was requested. Hypertrophy was discarded, but it showed

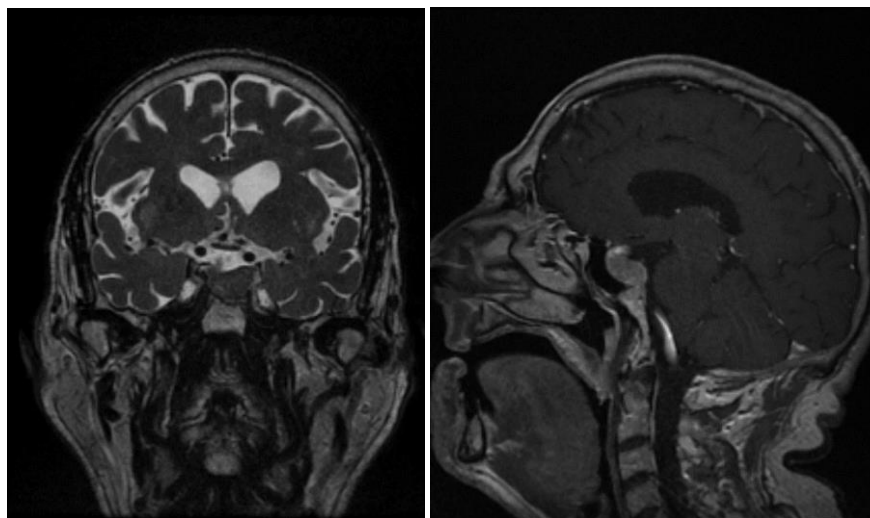
moderate mitral and tricuspid regurgitation with preserved ejection fraction.

Nowadays, the patient remains on Octreotide LAR 30 mg every 28 days together with Cabergoline. The last control MRI is from March 2019 showing radiological stability (Figure 5) with a size of  $19 \times 13 \times 21$  mm (Volume = 2,712

cc), similar to 2017 control (Figure 4). No signal changes were observed in T2 that could condition different response to SSA [6]. The blood test shows controlled thyroid function with TSH of 2.55 mUI / L and T4L 1 ng / dL together with IGF1 of 258  $\mu$ g / L (+3.25 SD adjusted for age). The patient remains stable without new symptoms. He has not required surgery.



**Figure 4:** MRI T1 sequences with gadolinium and T2 sequences of 2017.



**Figure 5:** MRI T1 sequence with gadolinium and T2 sequence of 2019.

### 3. Discussion

This case report presented a TSH-producing macroadenoma with 12 years of follow-up, showing co-secretion with GH in the last years. Approximately 70% of TSHomas only secrete TSH with a 30% mixed secretion with Prolactin or GH (16%) [1]. Furthermore, these tumors usually appear in the form of macroadenomas that invade the perisellar structures [7]. Regarding clinical symptoms, a percentage may be asymptomatic, although the most frequent symptoms will be derived from hyperthyroidism, chiasmatic compression, or hormonal involvement of the rest of the pituitary [1]. Up to 65% may associate an increase in thyroid size [8]. Our patient presented the symptoms of weight loss and the presence of a multinodular goiter on neck ultrasound without any changes related to the mass effect and without involvement of other pituitary axes.

Typical laboratory manifestations are elevated T3L or T4L with abnormally high TSH [1]. Analytical confirmation is

based on a suppression test. Although T3 suppression is indicated, it may be contraindicated in older patients with comorbidities [9]. Stimulation with 200 µg of TRH would be the main alternative, causing TSH to not rise in 85% of patients with TSHoma [7]. After the analytical confirmation, a turkish chair MRI should be performed to look for the adenoma [5]. In our case, we did not have the initial T3L value, which was probably high, conditioning the patient's weight loss.

As previously indicated, the recommended treatment consists of removal of the adenoma [5]. According to the series [4, 9-14], surgery achieves euthyroidism in 80% of patients. The surgery has her own implicit complications and with macroadenomas, hypopituitarism can be an undesirable consequence. Regarding medical treatment, drugs can be used for the symptomatic control of hyperthyroidism [15]. The SSAs, due to the over-expression of somatostatin receptors in these tumors [16], may play a role before and after surgery in case of lack of

control [17]. In some cases, it may be necessary to perform a total thyroidectomy to control hyperthyroidism [18].

In patients, such as ours, in whom surgery is rejected or contraindicated, two lines of treatment may be recommended. On the one hand, radiotherapy [5, 19] and, on the other, the SSAs that manage to restore hormonal control of the thyroid axis in 95% of cases, as well as a significant decrease in the size of the adenoma around 50% [7]. This control can be observed in the first 3 months of treatment [20]. In our case, the hormonal control was excellent from the beginning and regarding the size, a decrease of 3 mm could be seen in each axis of the adenoma that was mostly maintained during the follow-up.

Based on what we observed in the follow-up, it seems that the dose received by our patient of Octreotide LAR 30 mg every 28 days maintains hormonal control and tumor size stable after the initial reduction. Our case stands out for the progressive appearance of high IGF-1 values despite treatment with SSA, confirming non-suppression of GH with an oral glucose overload test. This co-secretion over time has been previously reported in another case treated with SSA without surgery [21] although the appearance of elevated GH was 12 months after starting treatment. Unlike our case that happened several years after and confirmed 2 years ago.

Hormonal co-secretion is explained by its dependence on the PIT-1 [22] factor. Back in 1989 the appearance of secretion granules with TSH and GH within the same adenoma cells is demonstrated [23]. The authors of the previously described case consider, however, that it could be a subpopulation of cells that are resistant to the action of SSA and, due to local changes caused by the sensitive cells, the autonomous production of GH is triggered [21]. The

evolution of our case seems to go against this theory since resistant cells are unlikely to remain dormant for so many years. We neither had an excess of GH at diagnosis reason why we discarded the initial co-secretion. It could also be a tumor dedifferentiation that leads to this co-growth, but it seems unlikely in our case given the stability and appearance of the pituitary adenoma. We propose as a possible mechanism the acquisition of resistance to SSA over time. Unfortunately, we do not have a biological sample to study this phenomenon.

However, the data suggests that the leak to SSA occurs progressively and, although the diagnosis is made in 2018, it seems to have been in progress since at least 2016. Treatment with Cabergoline (as has been done in other series [20]) seems to have improved IGF-1 values to optimal levels. Given the advanced age of our patient, in addition to the limited symptoms or associated comorbidity to excess GH, the surgery could be avoided. We are tracking the IGF-1 values in order to decide dosage changes of Cabergoline or SSA.

#### **4. Conclusions**

Thyrotropinomas are rare pituitary adenomas. Hormonal co-secretion is observed with some frequency either analytically or immunohistochemically, and their surgical treatment is usually effective. The appearance of late GH co-secretions that escape the control of analogues has been observed in cases with SSA-based treatment therefore we recommend its active screening during the follow-up of thyrotropinomas. A longer-term follow-up and more cases are needed to draw firm conclusions about this phenomenon.



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