CLINICAL CASE

TIMING OF SURGICAL APPROACH ON PATIENTS WITH SOMATOTROPINOMA AND DIFFERENTIATED THYROID CANCER

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Abstract

Acromegaly is a rare chronic, progressive disease caused by the increased secretion of growth hormone (GH) and subsequently insulin-like growth factor 1 (IGF-1). Benign thyroid overgrowth is a common phenomenon in this pathology, but some studies revealed that acromegaly is associated with an increase in the prevalence of malignant thyroid nodules. We present two cases of acromegaly associated with papillary thyroid carcinoma. A 69-year-old female accused at the age of 43 headache, enlarged hands and feet, secondary amenorrhea. The investigations revealed high IGF-1 and GH levels and a pituitary GH producing macroadenoma. 19 years after transsphenoidal adenomectomy, a multinodular goiter with areas of calcifications and intra and perinodular vascularization were discovered. Total thyroidectomy was performed and histopathology highlighted a papillary thyroid carcinoma. A 53-year-old male was admitted at the age of 45 with intense headache, dizziness, sexual dysfunction and a multinodular goiter. Clinical signs of acromegaly were correlated to the presence of an intra-sellar tumor with extension to the optic chiasm. Transsphenoidal adenomectomy was first decided and it was followed by conventional radiotherapy, somatostatin analogue and GH blocker afterwards. For multinodular goiter a fine needle aspiration showed the need of total thyroidectomy which was further performed and a minimally invasive papillary microcarcinoma was confirmed. The relationship between acromegaly and thyroid carcinoma could be related to the stimulatory effects of long-lasting excess of IGF-1 and GH on TSH induced thyroid cellular growth. Therefore, it is necessary to carry out effective treatment and periodic thyroid ultrasound examination in patients with acromegaly; usually thyroidectomy follows hypophysectomy to achieve GH control first.

Keywords*: acromegaly, papillary thyroid cancer, thyroid ultrasound, multinodular goiter, hypophysectomy*

Introduction

Acromegaly is a chronic disease resulting from excessive secretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) characterized by an overgrowth of acral parts of the body and different organs as heart, liver, thyroid nodules and cardio-metabolic impairment [1,2]. Long term exposure to GH and IGF-1 induces proliferative capacity and

potential malignancies as described in intestines, brain, breast, thyroid, uterus, prostate, kidney and skin [3-5]. Their reported prevalence is 4.7–11%, especially in patients with long-lasting uncontrolled acromegaly, longer than 5 years [6-9]. Chronic excess of IGF-1 stimulates the proliferation of cells and induces an anti-apoptotic effect in different types of cells and tissues, including the thyroid cancer cells [6-9]. Several studies have reported a high frequency of thyroid cancer mostly papillary thyroid cancer (PTC) in patients with acromegaly [9-11]. As thyroid follicular cells express IGF-1 receptors and IGF-1 is well recognized growth factor for thyrocytes, thus it may act in development of thyroid cancer in acromegalic patients [12[-14]. The actual incidence of thyroid cancer in patients with acromegaly and the impact of active acromegaly on the development of thyroid cancer is unknown but it is recognized that controlling the pituitary disease (including surgery) is the first step in managing both conditions followed by thyroid removal [12-14]. Therefore, it is necessary to carry out effective treatment in order to decrease the prevalence of malignancies and mortality, even if specific recommendations for ultrasound screening have not been included in recent guidelines [15,16]. We introduce a series of two patients diagnosed with acromegaly and differentiated thyroid cancer to whom pituitary and thyroid surgery was sequentially performed.

Case report 1

A 69-year-old non-smoking female, with positive family history for diabetes mellitus (brother) accused at the age of 43 dizziness, headache, enlarged hands and feet, enlarged facial features with macroglossia, and prognathism, fatigue and muscle weakness, secondary amenorrhea. The hormonal profile revealed high levels of IGF-1 and GH without suppression during a glucose tolerance test (OGTT) (Table 1).

A pituitary macroadenoma of 2 cm was visualized on MRI (Magnetic Resonance Imaging). Transsphenoidal hypophysectomy was performed during the same year. The procedure went well without any complications. She was hospitalized for 7 days. No therapy was given after discharge. The pathological report confirmed a somatotropinoma. One year later, the hormonal tests showed active disease and the presence of a tumor rest of 0.4 cm on pituitary MRI. Further conventional fractionated radiotherapy was applied. Gonad insufficiency diagnosed before surgery relapsed after radiotherapy. She was followed for 14 years when therapy with somatostatin analogue (octreotide LAR) was started because of active disease (20 mg per month and later 30 mg per month). At that point, thyroid ultrasound showed an enlargement with multinodular appearance (nodules of 1 to 2 cm), areas of calcification, and intra-nodular and peri-nodular vascularization (Figures 1,2).

Parameter	Patient's value	Normal Limits	Units
Before pituitary surgery			
GH	4.75*	<1	ng/mL
IGF-1	601	40-244	ng/mL
FT4	1.46	0.89-1.76	ng/dL
TSH	1.2	0.4-4	µUI/mL
FSH	1.4	1.7-7.7	mUI/mL
After hypophysectomy			
GH	3.73*	<1	ng/mL
IGF-1	266	40-244	ng/mL
FT4	0.9	0.89-1.76	pmol/L
TSH	0.56	0.4-4	µUI/mL
FSH	0.8	1.7-7.7	mUI/mL
7 years after thyroidectomy (current evalution)			
GH	0.825*,**	<1	ng/mL
IGF-1	39.94**	27-228	ng/mL
FT4	1.43***	0.89-1.76	ng/dL
TSH	0.49***	04-4	µUI/mL
FSH	30.6	>40	mUI/mL

Table 1 - Case 1: hormonal profile of a 69-year old female who suffered hypophysectomy for acromegaly at age of 43 years and thyroidectomy for papillary thyroid microcarcinoma at age of 58 years

Tests revealed low values for FT4 of 0.49 ng/dL (normal levels are between 0.89 and 1.76 ng/dL) with normal TSH (Thyroid Stimulating Hormone) of 0.87 µUI/mL. Total thyroidectomy was indicated and performed at the age of 62. The procedure went well, without any intra and perioperative complications. Histopathology revealed a papillary thyroid carcinoma T1N0M0 without extra-capsular extension. No

hypoparathyroidism was confirmed. Iatrogenic post-operative hypothyroidism was not treated for the first 3 months after surgery to check the oncologic status by assaying blood thyroglobulin of 6.8 ng/mL (normal range after total thyroidectomy of < 0.04 ng/mL) in association with a TSH of 32.4 µUI/mL. Under these circumstances, whole body scintigraphy was not considered further necessary, and neither complementary 131I radioiodine treatment. Suppressive treatment with levothyroxine was started on a daily dose of 125 µg. She was followed for 7 years after thyroidectomy.

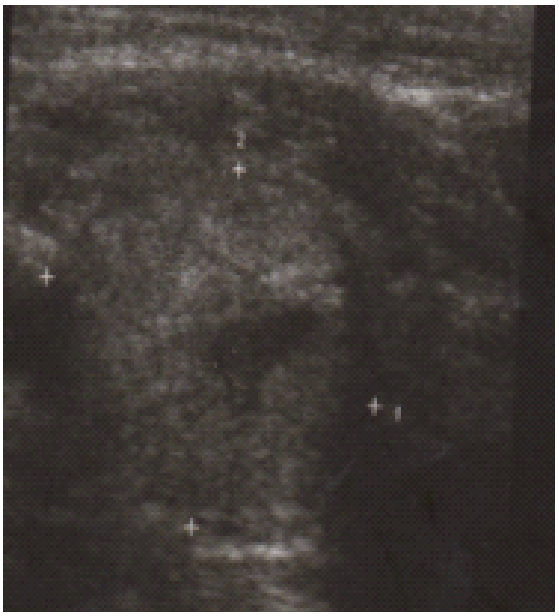

Figure 1 - Case 1: thyroid ultrasound (sagittal section: macronodule with microcalcifications area)

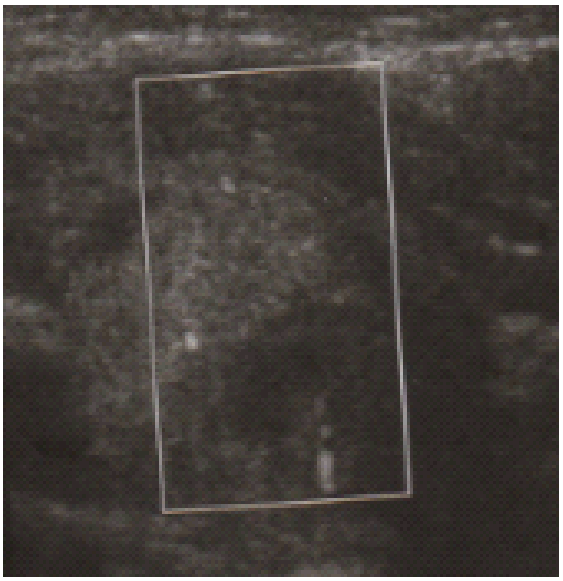

Figure 2 - Case 1: thyroid ultrasound (longitudinal section: macronodules with peri and intra-nodular vascularization)

The current assessment revealed adequate suppression of TSH under levothyroxine, normal values of IGF-1, and adequate suppression of GH during OGTT under treatment with 30 mg octreotide LAR per month. High blood pressure has been controlled by a double therapy including a beta blocker and an angiotensin- converting enzyme. Hyperlipidemia received specific medications consisting on statins and fenofibrate.

Case report 2

This is the case of a 53-year-old non-smoking male, with irrelevant family history, diagnosed with acromegaly at age of 45 (Table 2).

Parameter	Patient' s value	Normal Limits	Units
Before pituitary surgery			
GH	17.2*	<1	ng/mL
IGF-1	1053	66-225	ng/mL
PRL	98.8	98-456	µUI/mL
FT4	17.4	10.6-22.8	ng/dL
TSH	1.14	0.4-4	µUI/mL
After transsphenoidal hypophysectomy			
GH	2.9*	<5	ng/mL
IGF-1	667	66-225	ng/mL
FT4	15.1	10.6-22.8	pmol/L
TSH	<0.005	0.4-4	µUI/mL
After thyroidectomy (current evaluation)			
GH	2.79	<1	ng/mL
IGF-1	177.6*	66-225	ng/mL
FT4	20.8	10.6-22.8	
TSH	<0.005	04-4	µUI/mL
Testosterone	21.15	9.9-27.8	nmol/L

Table 2 - Case 2: the endocrine parameters in a 53-year-old male with acromegaly (hypohysectomy at age of 45 years) and papillary thyroid carcinoma (thyroidectomy at age of 46 years)

Clinical signs consisted of intense headache, visual disturbances, dizziness, sexual dysfunction, etc. Low levels for testosterone of 7.4 nmol/L (normal levels are between 9.9 and

27.8 nmol/L) confirmed central hypogonadism without secondary adrenal insufficiency (morning plasma cortisol of 254 nmol/L, normal between 172 and 497 nmol/L). MRI showed an intra-sellar tumor mass of 1.5 by 1 cm with extension to the optic chiasm and pituitary stalk (Figure 3).

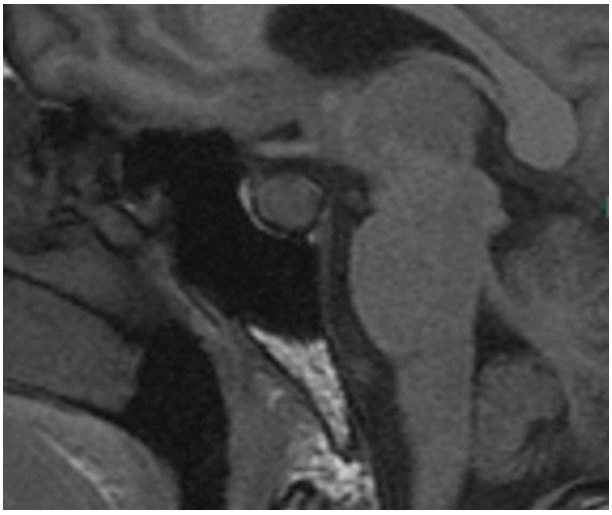

Figure 3 - Case 2: IV Contrast MRI performed preoperatively on a 45-year-old acromegalic male with intrasellar tumor of 1.5 by 1.0 cm contacting the optic chiasm and pituitary stalk (sagittal plane)

Transsphenoidal hypophysectomy was performed in the same year. No intra and peri-operative complications were reported. The patient was hospitalized for 5 days and after discharged. The first evaluation after pituitary surgery was done 3 months later and pituitary function was intact except for hypogonadism and intramuscular testosterone 1000 mg every three months was offered to the patient (Table 2). The acromegaly was still active in association with a remnant pituitary mass of 0.5 cm by 0.2 cm, thus conventional radiotherapy was performed. Also, somatostatin analogue octreotide LAR was continued for 2 years (progressively increasing doses of 20 mg per month to 30 mg per month) and then pegvisomant 20 mg daily was added. The patient has a history of multinodular goiter since the diagnosis of acromegaly. Thyroid ultrasound showed enlargement of the thyroid gland containing nodules bilaterally of 3.2 cm and 1.2 cm in the left lobe and 0.9 cm in the right lobe without radioiodine uptake at scintigraphy. Fine needle aspiration revealed cellular atypia. Thyroidectomy was recommended and delayed by the patient one year after pituitary surgery. He was hospitalized for 3 days. The procedure went well without incidents. The pathologic report showed minimally invasive papillary microcarcinoma T2N0M0. Post-surgery whole body scintigraphy (WBS) revealed thyroid remnants, hot spot in left thyroid lobe so 131I radioiodine treatment (86 mCi) was done. Levothyroxine therapy of 150 µg daily was continued for 1 year and then WBS was negative with decreased but not optimal thyroglobulin (a value of 10.2 ng/mL from 36.5 ng/mL after radioiodine ablative treatment, with normal between 3.5 and 77 ng/mL) so another radioiodine dose was reconsidered while acromegaly was controlled under specific medication.

Discussions

There are many reports suggesting the relationship between recurrent or active acromegaly and thyroid carcinoma [14,15]. Since pathogenic link via IGF1 and GH is possible, tide acromegaly control is needed, so first surgical control of acromegaly is needed and then thyroidectomy [15]. The first case had multinodular goiter since baseline but papillary thyroid carcinoma was emphasized 19 years after the diagnosis of acromegaly. The second case had the diagnosis of acromegaly and multinodular goiter established at the same time. In both cases at the time of thyroid cancer was confirmed the levels of GH and IGF-1 were increased, knowing the effect of IGF-1 excess of both benign and malignant cancerous changes [16] Even if in the first case the exposure to elevated levels of GH and IGF-1 was longer, a lower degree of cancer extension was confirmed, thus radioactive iodine ablation was no longer necessary. Also, in the female case, acromegaly control was achieved easier than in the male case. In the second case, the thyroid cancer extension required radioactive iodine therapy besides surgery while acromegaly control was achieved only after complex medical therapy. In patients with acromegaly, increased levels of IGF-1 enhance TSH induced thyroid cellular growth in normal thyroid cells and IGF-1 receptors were found to be present in neoplastic human thyroid tissues

[16,17]. A further mechanism by which IGF-1 may serve to promote the development of malignancy is inhibition of apoptosis [16,17]. It has been suggested that patients with sustained increased levels of IGF-1 should have their thyroid examined regularly, including undergoing an ultrasound-guided fine-needle aspiration biopsy, particularly of nodules which have worrisome features in ultrasonography [1,13,17]. In our cases, the thyroid ultrasound was performed as routine evaluation while fine needle aspiration was considered for the second case. More accurate and more frequent examination in patients with acromegaly could serve to earlier diagnosis and treatment of thyroid cancer.

Conclusions

Patients with acromegaly are at an increased risk of thyroid papillary cancer and baseline and periodic thyroid ultrasound examination in order to indicate thyroidectomy in cases at high risk. Therefore, it is necessary to carry out effective treatment in order to decrease the prevalence of malignancies and mortality while timing of thyroid surgery usually is after the pituitary approach.

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