Thyroid Papillary Carcinoma in a Case with Growth Hormone and Thyrotropin Secreting Hormone Co-Secreting Pituitary Macroadenoma

Büyüme Hormonu ve Tirotropin Salgılatıcı Hormon Birlikte Salgılayan Hipofiz Makroadenomu Olgusunda Saptanan Tiroid Papiller Kanseri

ABSTRACT We report a case of growth hormone and thyrotropin secreting hormone (GH/TSH) co-secretting pituitary macro-adenoma who was treated by trans-cranial surgery and gamma-knife radio-surgery and had been on somatostatin analogue therapy for four years and then she was diagnosed to have thyroid papillary carcinoma (TPC). Following total thyroidectomy, depending on her high insulin like growth factor-1 (IGF-1) and normal TSH levels ablation was planned with high dose radioiodine. However, that time recombinant TSH was not available in our country so radio-ablation was performed necessity. Any enlargement was observed in her residual pituitary tumor size since that time. Now she has been at the three and a half years of TPC follow-up and is free from the disease with unchanged pituitary tumor sizes.

Key Words: Thyrotropin-releasing hormone; growth hormone-secreting pituitary adenoma; thyroid neoplasms


Anahtar Kelimeler: Tirotropin salgılatıcı hormon; büyüme hormonu salgılayan pitüiter adenoma; thyroid tumours

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Papillary thyroid carcinoma in a case with thyrotropin secreting pituitary adenoma is a rarely reported co-presentation. There are many unidentified issues regarding its management, since there have been only five published cases in literature. One of them was treated by thyroidectomy followed by pituitary surgery, while other three subjects had the pituitary operation first.1-4 A recently published case had a growth hormone and thyrotropin secreting hormone (GH/TSH) co-secretting pituitary
adenoma and thyroid papillary carcinoma (TPC), just like our patient. It was reported that she refused to have a pituitary surgery and chose primary medical therapy with a somatostatin analogue (SA), and then had total thyroidectomy for TPC followed by recombinant human TSH (rhTSH)-stimulated radioactive iodine (RAI) remnant ablation with any enlargement in her pituitary tumor.\(^5\)

Herein, we report a case with GH and TSH co-secreting pituitary macroadenoma who exhibited multifocal thyroid papillary carcinoma during follow-up. She was treated with thyroidectomy followed by RAI remnant ablation with levothyroxine withdrawal. She experienced any sign or symptom regarding residual pituitary tumor growth.

**CASE REPORT**

A 61-year-old Caucasian female had been on follow-up due to a GH and TSH co-secreting pituitary macroadenoma for the last 42 months when she was diagnosed to have papillary carcinoma by fine needle aspiration biopsy (FNAB) of thyroid. At the very early times of her admittance, her pituitary tumor was found to cause optic tract compression, so following hormonal work-up, she was advised having surgery. The pituitary adenoma was found to secrete GH and TSH autonomously with any clinical sign. She had an operation transcranially and the pathological specimens were observed to be positive for GH and TSH at immunohistochemical examination. Details regarding the diagnostic procedure of the patient were published by us before.\(^6\)

She had unfortunately a bulky residual tumor and hormonally active disease after the surgical procedure. She started on somatostatin analogue (SA) therapy with long acting ocreotide (O-LAR) 30mg every 28 days. At the 14\(^{th}\) month of SA therapy, her plasma insulin like growth factor (IGF-1) was above age and sex-corrected levels; 235 ng/ml (70-197), where as basal GH was as desired; 0.63 ng/ml. Her thyroid function tests were also within normal limits; TSH:1.48 \(\mu\)IU/ml [(free tri-iodothyronine (T\(_3\)) and free thyroxine (T\(_4\)) within limits, as well]. Magnetic resonance imaging (MRI) of the pituitary exhibited any tumor regression. Then, she preferred having gamma-knife radio-surgery for the residual tumor tissue at another center.

At the 42\(^{nd}\) month of her follow-up, while she was on O-LAR 30mg every 28 days, her thyroid ultrasonography revealed multinodular goiter with a dominant nodule of 20x17x13 mm in size at the right lobe. A fine needle aspiration biopsy (FNAB) was done and the diagnosis of a papillary thyroid carcinoma was performed. When her medical records were examined retrospectively, she was observed to have another thyroid ultrasonography which was reported three years before. It exhibited similar nodule sizes when compared with the present one. Moreover, a FNAB was also performed to the dominant nodule mentioned above which was reported as “cellular nodule” that time.

Considering about her high IGF-1 and normal TSH levels which were all known to be potent growth factors for the thyroid follicular cell, the risk of leaving the autonomous pituitary TSH secretion without end-organ response was taken and a decision was made in favor of performing total thyroidectomy. The procedure was done without complication. The pathological analysis of the operation specimen exhibited thyroiditis with two areas of papillary carcinoma; 5x5 mm and 4x4 mm in size without capsule or vascular invasion (Figure 1). She was started on thyroxine suppression immediately after the surgery.

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**FIGURE 1:** Pathological examination of the thyroidectomy specimen exhibiting papillary formations and clear overlapping nuclei (Hematoxylin Eosin staining, 10x20).
The next decision to be made was whether to ablate the rest of the thyroid with high dose radioiodine or not. Her high IGF-1 and insuppressible normal TSH levels and multifocality of the thyroid tumor convinced us to perform high dose radio-ablation with $^{131}$I even though it was a microcarcinoma. Actually, the most logical approach was to perform recombinant TSH (rhTSH)-stimulated RAI remnant ablation. However, that time, recombinant TSH was not on the market in our country and naturally it was out of insurance coverage. Besides, the patient could not afford the cost of the drug personally.

She had been on follow-up for four years and had been taking SA therapy since then. She had had gamma-knife radio-surgery following transcranial surgery and for the last four years her residual tumor size had remained the same without progression. These all encouraged us to give the high dose radiiodine following thyroxine withdrawal. The patient was informed about the risks of tumor enlargement following hormone withdrawal. She approved and gave written consent.

On the 30$^{th}$ day of thyroxine withdrawal, her TSH reached up to 14.65 μIU/ml maximally and 100mci $^{131}$I was given to her orally. Post-therapy scan performed at the fifth day revealed iodine uptake only at the thyroid bed. She experienced any sign or symptom related to pituitary tumor enlargement. Control pituitary MRI exhibited stable tumor size with any further tumor growth. She continued to be followed up with monthly SA injections and daily thyroxine 200mcg. Six months later, Whole Body Scanning (WBS) with 3 mci iodine following thyroxine withdrawal exhibited any iodine uptake. Pituitary MRI remained the same.

It now has been three and a half years since the diagnosis of thyroid papillary carcinoma. She is taking high dose thyroxine daily and SA injections every sixty days. Her TSH levels are at low normal limits, thyroglobulin and anti-thyroglobulin levels are steadily going down. Her thyroid ultrasonographic examinations visualize any residual thyroid tissue and enlarged lymph node. Her growth hormone axis is under control as well as her residual pituitary tumor size at MRI.

Hormonal analyses of the case regarding the pituitary adenoma and thyroid papillary carcinoma were expressed in details chronologically in Table 1 and Table 2.

T1-weighted pituitary magnetic resonance images demonstrating original pituitary tumor size and stable residual tumor sizes during follow-up could be observed in Figure 2, 3 and 4 and 5.

A written informed consent was obtained from the patient for the use of her personal medical records.

## DISCUSSION

In current medical literature, this is the second case presented with simultaneous GH and TSH secreting pituitary macroadenoma and thyroid papillary carcinoma. More importantly, trans-cranially and

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<th>TABLE 1: Follow-up hormonal details of the patient.</th>
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<td>GH (ng/ml (0.0-5.0)</td>
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<td>IGF-1 (ng/ml (70-197)</td>
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<td>TSH (μIU/ml (0.30-4.94)</td>
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<td>Free T3 (pmol/L (2.22-5.34)</td>
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<td>Free T4 (pmol/L (9.0-25.0)</td>
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1NA: Not available
2at the 14th month O-LAR injections
33 mo after thyroidectomy she was on O-LAR 20 mg/month and levothyroxine 200 μg/day
4Last visit while she was on Lanreotide Autogel 120 mg every 60 days and levothyroxine 250 μg/day
(On October 2007 Somatostatin analogue had to be switched to Lanreotide Autogel from O-LAR due to precipitation of the drug possibly resulting from a break in cold chain transfer).
gamma-knife surgically treated pituitary residual tumor which had been on SA therapy for years since the diagnosis, exhibited any enlargement following high dose radioiodine ablation with thyroxine withdrawal. The thyroidal aspect of the present case is the main point we want to discuss in the following section. Giving details regarding the diagnosis of an autonomously TSH and GH co-secreting pituitary adenoma is out of the scope of this paper, and further information can be found in the original presentation of this case.6

At the initial diagnosis, the patient was referred to pituitary surgery due to classical bi-temporal hemianopsia detected at visual field analysis. Thyrotropin secreting pituitary tumors may present marked fibrosis which may be attributed to their high expression of basic fibroblast growth factor.8 Some adenomas are reported to be so hard that they are called as “pituitary stones”.9 Trans-sphenoidal surgery was obviously the preferred option for the present macroadenoma, however, the tumor was so hard that the surgeon had to move to trans-cranial approach intra-operatively. As it happened in many pituitary macroadenomas, the procedure was not curative; her postoperative IGF-1 was above limits and TSH was detectable.

Thyrotropin and IGF-1 are well-identified growth factors for thyroid follicular cells.10,11 Accordingly, cases that have autonomous secretion of such growth factors should be screened for thyroid nodules with thyroid ultrasonography. Our patient is a solid evidence for this recommendation. She had two different fine needle aspiration cytology results which were first reported as “cellular nodule” and then “papillary carcinoma” in the presence of stable nodule sizes in a three years time. We share the opinion of Nguyen and colleagues advising total thyroidectomy for TSHoma cases har-
boring thyroid nodules regardless of their cytological findings.\textsuperscript{5}

The timing of thyroidectomy is a question of debate. Fear of enlargement in unopposed thyrotrophin secreting adenoma is the underlying problem, because a small decrease in thyroid hormones may result in hyperproliferation of autonomous thyrotrophs.\textsuperscript{12} Depending on our experience, we believe that thyroidectomy should be performed after the control of pituitary tumor size and function. Nevertheless, we can not comment on how long it takes for such a tumor to be considered as under control. We are aware of the fact that we were lucky as the thyroid tumor was detected at the fourth year of follow-up and the residual pituitary tumor exhibited stable sizes reminding that it might be fibrotic in origin after all these therapeutic procedures.\textsuperscript{13} These all encouraged us not only to perform total thyroidectomy, but also to give ablative doses of radiiodine without rhTSH stimulation which was no doubt the method of choice if we could achieve the drug.

In conclusion, the present case clearly demonstrates that the thyroid nodules in TSHoma cases should not be ignored. Total thyroidectomy followed by radio-ablation via thyroxine withdrawal may be safe with any further pituitary residual tumor enlargement in selected patients.

FIGURE 4: Pituitary MRI (coronal contrast-enhanced T1 weighted image). After high dose RAI ablation.

FIGURE 5: Pituitary MRI (coronal contrast-enhanced T1 weighted image). Control visit.


