

## Subacute Thyroiditis Following Treatment for Cushing Syndrome

*Cushing Sendromu Tedavisi Sonrası Gelişen Subakut Tiroidit Olgusu*

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Thyroid diseases frequently accompany Cushing syndrome (CS). Nodular or diffuse goitre and autoimmune thyroid diseases may be evident during or after treatment of CS. A 29-year-old female presented with weight gain, hypertension and hirsutismus. Examinations revealed hypercortisolemia. Computed tomography revealed a solid mass 2.5-3 cm in size in the left adrenal gland and adrenalectomy was done. The diagnosis was adrenal cortical adenoma. A few days later she complained of pain in the left ear, neck, and head, which was diagnosed as subacute thyroiditis. To our knowledge, subacute thyroiditis accompanying CS is not reported in the literature before.

**Key Words:** Adrenalectomy; Cushing syndrome; thyroiditis subacute.

Tiroid hastalıkları sıkılıkla Cushing sendromuna (CS) eşlik ederler. Nodüler veya diffüz guatr ile otoimmün tiroid hastalıkları, CS'nin seyrinde veya bu nedenle tedavi gördükten sonra ortaya çıkabilir. Yirmi dokuz yaşında kadın hasta kilo alımı, hipertansiyon ve hirsutismus nedeniyle başvurdu. İncelemeler sonucu hiperkortizolemi saptandı. Bilgisayarlı tomografide sol surrenal glandda 2.5-3 cm çapında kitle görüldü ve adrenalektomi yapıldı, adrenal kortikal adenoma tanısına varıldı. Birkaç gün sonra ortaya çıkan sol boyun, kulak ve baş ağrısının değerlendirilmesi sonucu subakut tiroidit tanısı konuldu. Literatürde daha önce bildirilmiş CS'ye eşlik eden subakut tiroidit olgusuna rastlanmamıştır.

**Anahtar Sözcükler:** Adrenalektomi; Cushing sendromu; subakut tiroidit.

Thyroid stimulating hormone (TSH) secretion is primarily controlled by circulating thyroid hormones. TSH is released in a pulsatile manner from the thyrotrope cells of the anterior pituitary gland. Cushing syndrome (CS) is characterized by several multiple complex metabolic and endocrine alterations. Thyroid diseases frequently accompany CS. Nodular or diffuse goitre may

be evident; impaired thyroid function tests (TFT) and positive antibody titers due to autoimmune thyroid diseases can also be observed. Antibody positivity is more common after treatment of CS; even antibody titers increase and flare-ups of autoimmune thyroid diseases may be seen.<sup>[1-7]</sup>

In CS, TSH secretion is mainly adjusted by cortisol. Thyrotropin releasing hormone (TRH)

release is impaired in CS and in patients taking supraphysiologic doses of steroids.<sup>[8-13]</sup>

Thyroid stimulating hormone response to TRH is blunted. Consequently basal TSH is decreased; besides circadian rhythm and pulsatile release is abolished. It has been shown that patients with CS have basal TSH and TSH response to TRH, inversely correlated with plasma cortisol and urinary excretion of free cortisol.<sup>[14]</sup> Nonthyroidal illness syndrome (NTIS) may contribute to the depressed level of TSH in CS; TSH suppression is more prominent. In healthy subjects TSH suppression following dexamethasone administration indicates that TSH suppression in CS cannot be attributed solely to NTIS.<sup>[12]</sup>

We present a case with subacute thyroiditis following treatment for CS which is, to our knowledge, not reported in the literature before.

### CASE REPORT

A 29-year-old woman was admitted to the Division of Endocrinology and Metabolism of Trakya University School of Medicine in 2003 due to weight gain (approximately 15 kg), hypertension and hirsutismus for six months. She also complained of cessation of menses and

tingling in her hands and feet for the last three months. She used no drugs other than amitriptyllin and citalopram for depression. She was smoking one packet a day. She had a baby four years ago.

Physical examination revealed nothing but obesity and hirsutismus (Ferriman-Gallway score 10). Her blood pressure was 130/80 mmHg. She weighed 85 kg, was 1.64 m tall, and her body mass index was 32 kg/m<sup>2</sup>. Her waist and hip circumference was measured as 107 cm and 111 cm, respectively. Waist-hip ratio was calculated as 0.96. Fasting plasma glucose, renal, and liver function tests as well as TFT were normal. LDL-cholesterol was 156 mg/dL, total cholesterol 248 mg/dL, and triglyceride 195 mg/dL. Leukocyte count was 11500/mm<sup>3</sup> with a left shift. Electrolyte imbalance was absent.

Weight gain, hirsutismus, and a history of hypertensive attack led us to search for hypercortisolemia (Table 1). Low ACTH, high basal cortisol, loss of diurnal rhythm of cortisol secretion, absence of suppressibility of cortisol in 1 mg overnight dexamethasone test and low dose (0.5 mg q6h for 8 doses) dexamethasone suppression test (LDDST) proved hypercorti-

**Table 1. Biochemical tests preceding adrenalectomy**

	Preoperative tests	Normal values
Basal cortisol (µg/dL)	29.2	5-25
Midnight cortisol (µg/dL)	27.9	
LDDST cortisol (µg/dL)	25	<1.8
HDDST cortisol (µg/dL)	27.5	<50% of baseline value
ACTH (pg/mL)	10	0-46
Anti TG (IU/mL)	20	0-40
Anti TPO (IU/mL)	10	0-35
Prolactin (ng/mL)	6.9	1.9-25
DHEA-SO <sub>4</sub> (µg/dL)	30	35-460
Free testosterone (ng/dL)	2.59	0.06-2.57
TSH (IU/mL)	0.404	0.4-4
Free T <sub>3</sub> (ng/dL)	1.12	1.8-5
Free T <sub>4</sub> (pg/mL)	0.96	0.8-1.9
75 g glucose OGTT 2 <sup>nd</sup> hour (mg/dL)	139	<140

LDDST: Low-dose dexamethasone-suppression test; HDDST: High-dose dexamethasone suppression test; ACTH: Adrenocorticotropic hormone; Anti TG: Antithyroglobulin; Anti TPO: Antithyroid-peroxidase; DHEA-SO<sub>4</sub>: Dehydroepiandrosterone sulphate; TSH: Thyroid stimulating hormone; OGTT: Oral glucose tolerance test.

**Table 2. Biochemical tests following adrenalectomy**

	20 days	45 days	2 months	3 months	5 months	7 months	26 months
Basal cortisol ( $\mu\text{g}/\text{dL}$ )	12					5	12.2
ACTH ( $\text{pg}/\text{mL}$ )	26.4						21.1
TSH ( $\text{IU}/\text{mL}$ )	0.039	0.043	0.012	0.185	7.28	2.8	2.01
Free T3 ( $\text{ng}/\text{dL}$ )	7.08	8.39	13.4	6.67	6.71		
Free T4 ( $\text{pg}/\text{mL}$ )	1.62	1.85	1.38	0.73	0.87	1	1.09
Anti TG	20 $\text{IU}/\text{mL}$						
Anti TPO	10 $\text{IU}/\text{mL}$						

ACTH: Adrenocorticotrophic hormone; TSH: Thyroid stimulating hormone; Anti TG: Antithyroglobulin; Anti TPO: Antithyroid-peroxidase.

solemia. High dose (8 mg dexamethasone as a single oral dose) dexamethasone suppression test (HDDST) indicated surrenal glands responsible for CS. Abdominal computed tomography revealed a solid mass 2.5-3 cm in size in the left surrenal gland. Osteoporosis was evident on dual energy X absorptiometry.

Left subtotal adrenalectomy was done. The tumour was surrounded by a thin fibrous capsule and well demarcated from the surrounding normal adrenal gland on macroscopic examination. Histopathologic examination showed two groups of cells; one with round-oval nucleus and broad cytoplasm and the other with round-oval nucleus and dark eosinophilic granules. No mitosis was observed. These features were compatible with adrenal cortical adenoma.

On the fourth day of operation intravenous ampicillin-sulbactam at a dosage of 6 g/day and oral-parenteral nonsteroid antiinflammatory drugs were begun due to high fever (39 °C). Hyperemia along the incision line suggested infected wound. As a result ultrasonography was performed. Fluid collection underneath the incision line reached 1.5 cm depth. The incision line was explored. Serohaemorrhagic fluid instead of suspected purulent fluid was detected. However, cultures of urine, blood, and the fluid collection were negative.

A few days later she complained of severe pain in the left ear, neck, and head. Ear and neck was tender. Ear-nose-throat specialist found no pathology except tenderness. Thyroid hormones were reevaluated; TSH was low in contrast to high levels of FT<sub>3</sub>. Erythrocyte sedimentation

rate (ESR) was 92 mm/h (Table 2). Neck ultrasonography had revealed thyromegaly (right thyroid lobe 55x25x19 mm and left lobe 56x27x15 mm) and hypoechoic semisolid nodule in the middle portion of the left lobe which was measured to be 12x8.5 mm in size. Very low uptake was evident on I131 thyroid scintigraphy. Thyroid autoantibody titers (antithyroglobulin [Anti TG], antithyroid-peroxidase [Anti TPO]) were normal. These findings suggested subacute thyroiditis. Therefore, thionamides were not begun and only 40 mg per day propranolol oral therapy was held. On the 20th day of surgery, cortisol was also evaluated and found normal. Hyperthyroidism continued on visits following adrenalectomy (45 days, 2 months and 3 months after surgery). Three months after surgery TFT and ESR (16 mm/h) returned to normal. She entered hypothyroidic phase on the fifth month. Thyroid function tests as well as cortisol on the seventh month of surgery were normal. Our patient was clinically well and cortisol and thyroid hormone levels were normal until she was last seen in November 2005.

## DISCUSSION

In this report, hyperthyroidism which ensued after curative subtotal adrenalectomy for CS due to adrenal adenoma is evaluated.

Following the surgery, severe pain in the neck occurred. Thyroid function tests indicated a hyperthyroidic state. Ear-nose-throat examination did not obviate a cause. Pain in the thyroid region, increased ESR, and very low uptake in I131 thyroid scintigraphy led to a differential diagnosis of subacute thyroiditis. Suppurative thyroiditis was

also considered, although it is a rare disorder. Fever is easily controlled by one group of antibiotic, cultures were fruitless, there was no abscess formation, and the state did not require a surgical drainage approach. These outlined features were not components of suppurative thyroiditis. Furthermore TFT is usually normal in suppurative thyroiditis in contrast to the 4.5 months' duration of hyperthyroidic state of our case.

Subacute thyroiditis does not have an autoimmune basis. Rare cases develop TSH receptor antibodies (TRAb) thereafter.<sup>[15]</sup> Low titers of thyroid autoantibodies before surgery and no increase after surgery did not support an autoimmune thyroid disease. Although TRAb was not studied; low titers of Anti TG and Anti TPO, very low uptake in I<sup>131</sup> thyroid scintigraphy, and absence of ophthalmopathy and previous hyperthyroidic attacks did not align with Graves disease.

Corticosteroids exert antiinflammatory and immunomodulatory effects on various tissues<sup>[16]</sup>. Withdrawal of endogenous hypercortisolism probably might have been operational in mounting this inflammatory process.

Acute illness or injury can also precipitate thyrotoxicosis. There is almost always an underlying thyroid disease. The patient is usually short of therapy or have an undetermined hyperthyroidism which is exacerbated after a following medical or surgical stress. Our patient had no known history of thyroid disease, TFT preceding adrenalectomy was normal and there was a new-onset hyperthyroidic state after the surgery. Her past and antibody negativity did not fit into an autoimmune picture.

Subacute thyroiditis is usually due to a viral origin, but other infectious agents may be also involved. Microbiologic studies for isolating the offending agent are usually cumbersome and are not deemed necessary for diagnosis. There is evidence for sensitization of T lymphocytes against thyroid antigen which is most likely due to inflammation<sup>[17]</sup>. While fever preceded thrombophlebitis and cultures yielded no positive results, neck pain and increased ESR suggested subacute thyroiditis. Whether a probable non

defined infectious agent or surgery induced systemic inflammation led to sensitization against thyroid antigen and consequent thyroiditis is open to discussion.

The clinical picture ranged from nodular goitre and euthyroidism to subacute thyroidism ensued after curative therapy of CS. This cascade of events show that thyroid and cortisol are linked to each other closely and their related diseases may interact. The clinical picture may be a challenge to the physician. Since subacute thyroiditis neither accompanying nor occurring after CS has been reported in the literature before, we think that our case demands attention.

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