

Differentiated thyroid cancer is one of the most common endocrine cancers. Typical standard treatment includes total thyroidectomy with partial lymphadenectomy, then depending on the indications, treatment with iodine isotope ^{131}I . A prerequisite to conduct the therapy is to obtain endogenous thyroid-stimulating hormone (TSH) stimulation ($\text{TSH} > 30 \mu\text{U/ml}$). We describe two patients with differentiated thyroid carcinoma in whom no rise in serum TSH was observed after withdrawal of thyroxine. In one patient TSH deficiency was due to partial hypopituitarism secondary to a tumor of the pituitary gland. In the second patient the TSH level was suppressed by metabolically active thyroid tissue with bilateral ovarian teratomas. The problems with TSH growth after withdrawal of thyroxine requires additional studies to identify the cause. Above two possible reasons for the lack of TSH stimulation after withdrawal of thyroxine were presented. In the case of non-TSH stimulation due to hypopituitarism both control tests and isotope treatment should be carried out using stimulation by recombinant human TSH (rhTSH).

Key words: differentiated thyroid cancer, TSH stimulation.

Lack of TSH stimulation in patients with differentiated thyroid cancer – possible causes

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Introduction

Differentiated thyroid cancer is one of the most common endocrine cancers. Women suffer 2–3 times more often than men. Morbidity in Europe varies in the range 1.4–5.0/100 000/year. Thyroid cancer usually does not cause thyroid dysfunction, and does not result in hyperthyroidism or hypothyroidism. Occasionally hyperthyroidism may occur in a patient with follicular carcinoma, especially of metastatic follicular carcinoma. Standard treatment includes total thyroidectomy, then depending on the indications treatment with iodine ^{131}I . Each operation of thyroid cancer should routinely include resection of central neck lymph nodes – laryngeal anterior, tracheal anterior and posterior. Isotope therapy uses the special feature that cancer cells, like the healthy thyroid tissue, have the ability to take up and accumulate iodine. Diagnosis and treatment of iodine isotope must be carried out under conditions of adequate endogenous TSH stimulation. The levels should not be less than $30 \mu\text{U/ml}$. This stimulation is achieved by approximately four weeks of levothyroxine withdrawal. In recent years recombinant human TSH (Thyrogen) was introduced to stimulate iodine uptake of thyroid. This enables the diagnosis and radioiodine therapy without discontinuation of thyroxine. Exogenous stimulation with Thyrogen is primarily used in patients with thyroid cancer metastases, but also in patients with partial or complete hypopituitarism in whom endogenous stimulation is impossible. Below we present cases of two patients in whom despite thyroxine withdrawal, no increase in TSH was obtained.

Case number 1

A 59-year-old woman after total strumectomy due to papillary thyroid carcinoma ($\text{pT}_{1\text{a}}, \text{N}_0, \text{M}_0$) was admitted to the Department of Endocrinology to provide an ablative dose of radioactive iodine. Despite the 4-week thyroxine withdrawal, serum TSH was $7.24 \mu\text{U/ml}$ (normal $0.27\text{--}4.2 \mu\text{U/ml}$) with normal concentrations of free hormones (fT_3 4.98 pmol/l , fT_4 12.09 pmol/l). In ultrasonography of the neck thyroid tissue in the thyroid bed with dimensions $11 \times 13 \times 20 \text{ mm}$ was detected. Serum concentration of thyroglobulin was 102.7 ng/ml , autoantibodies against Tg (anti-Tg) 30 U/ml . In the study of whole-body scintigraphy with ^{131}I , out of focus tracer accumulation in the thyroid bed, there were no further outbreaks of tracer uptake. In the imaging studies of the neck and chest metastases were not found. Gynecological ultrasound revealed the presence of bilateral ovarian tumors with dimensions $6 \times 4 \text{ cm}$ in the right ovary, $7 \times 3 \text{ cm}$ in the left one. Due to the lack of TSH stimulation radioiodine treatment was abandoned. The patient underwent gynecological surgery – total hysterectomy with appendages was performed. Histopathological diagnosis was bilateral ovarian teratomas with the presence of thyroid tissue. The patient was re-admitted to the Department of Endocrinolo-

gy for subsequent radioactive iodine therapy. After 4-week levothyroxine withdrawal the following results were obtained: TSH 36.34 μ U/ml, Tg 16.85 ng/ml, aTg 24 U/ml. The patient received 150 mCi of ¹³¹I, then suppressive doses of thyroxine. Diagnosis after a control period of 12 months is currently planned.

Case number 2

A 71-year-old patient with papillary cancer of the thyroid gland (pT₂,N₀,M₀) after thyroidectomy and subsequent ablative ¹³¹I treatment was admitted to the Department of Endocrinology in order to perform control tests on TSH stimulation. Despite the 4-week thyroxine withdrawal, TSH stimulation could not be achieved (TSH 4.68 μ U/ml) despite the concentration of free hormones being below the normal range (fT₃ 0.54 pmol/l, fT₄ 2.17 pmol/l). In additional studies, there was no TSH response in the TRH stimulation test, and also reduced serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), normal levels of adrenocorticotropic hormone (ACTH) and human growth hormone (HGH), and elevated level of prolactin (PRL) (1026 μ U/ml). MRI of the pituitary confirmed the presence of a 34 × 18 × 16 mm tumor in this gland, growing into the sella turcica and infiltrating both cavernous sinuses (Fig. 1). The ophthalmic examination revealed typical bitemporal reduction of vision. Due to the size of the pituitary macroadenoma and invasion of cavernous sinus walls, neurosurgery was abandoned. Dopamine agonists (bromocriptine) are used to yield a significant decrease in the level of prolactin. Control tests were done with the use of exogenous stimulation by recombinant human TSH giving two doses of thyrotropin alfa, each one 0.9 mg, at an interval of 24 hours. Whole-body scintigraphy showed no pathological tracer accumulation foci, with low concentrations of Tg and anti-Tg.



Fig. 1. MRI of the head. The apparent pituitary macroadenoma

Discussion

After total thyroidectomy due to differentiated thyroid cancer the next step of the treatment, in most cases, is treatment by radioiodine isotope therapy with the use of ¹³¹I. TSH stimulation is needed to increase the uptake and accumulation of the isotope in the tumor. That is why 3–4 weeks of levothyroxine withdrawal is planned before the therapy.

The patient in the first case failed to obtain an increase in TSH, despite the 4-week thyroxine withdrawal, due to the presence of metabolically active thyroid tissue within bilateral ovarian teratomas. Teratomas are relatively common tumors of the ovaries, recognized in about 15–20% of cases of ovarian neoplasms [1, 2]. In about 15% of cases teratomas contain thyroid tissue [3, 4] which may (rarely) cause symptoms of hyperthyroidism [5, 6]. After hysterectomy with appendages the patient successfully obtained TSH stimulation and a significant decrease of thyroglobulin was observed, which indicates the presence of metabolic activity of thyroid tissue in the structure of the teratoma.

In the second case no TSH stimulation during the control tests was surprising, because while ablative therapy after 4-week discontinuation of L-thyroxine had been done TSH had risen up to 32.44 μ U/ml. It turned out that lack of TSH stimulation was due to partial hypopituitarism in the course of tumor of the pituitary gland [7–9]. Since 1993 recombinant human TSH – Thyrogen, produced by the company Genzyme – has been commercially available. Application of Thyrogen allows diagnostics to be performed in patients with differentiated thyroid carcinoma and lack of endogenous TSH stimulation due to hypopituitarism [10, 11]. This procedure was used in the patient and no pathological tracer accumulation in the whole-body scintigraphy was observed. Additionally an appropriate concentration of Tg was found.

Above two possible reasons for the lack of TSH stimulation after withdrawal of thyroxine were presented. Lack of TSH growth after withdrawal of LT 4 requires additional studies to identify the cause. In the case of non-TSH stimulation due to hypopituitarism, both control tests and isotope treatment should be carried out using recombinant human TSH (rhTSH).

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