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Journal of Radiology & Radiation therapy

Case Report

Challenges in the Suppression of Thyroid Stimulating Hormone in a Thyroid Cancer Patient with Chronic Renal Failure

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Abstract

Thyroid stimulating hormone (TSH) suppression therapy with excessive administration of thyroxine (levothyroxine sodium; T4) is commonly initiated after surgical removal of differentiated thyroid carcinoma (DTC) to delay metastasis progression. In the present report, we describe a case with chronic renal failure (CRF) and poor TSH control despite sufficient T4 administration for TSH suppression. A 37-year-old man had been managed with insulin therapy and modified diet for the treatment of diabetes complicated with diabetic eye disease and diabetic nephropathy. He underwent total thyroidectomy and neck dissection for multiple cervical lymph node (LN) metastases from thyroid cancer and was referred to our hospital for two sessions of I-131 radioiodine therapy (RIT). For TSH suppression therapy, he received 125 μg/day of T4 orally. A blood test at initial admission indicated that the fT3 levels were 2.0 (normal range, 2.6–4.2) pg/mL, fT4 levels were 1.0 (0.9–1.7) ng/mL, TSH levels were 48.8 (0.32–4.04) μIU/mL, and thyroglobulin (Tg) levels were 73.8 (0–30) ng/mL. The test for anti-thyroglobulin antibody yielded negative results and the creatinine (Cr) levels were slightly elevated at 1.24 mg/dL (normal range, 0.5–1.1). Due to the high levels of TSH observed, the T4 dosage was increased from 125 μg/day to 150 μg/day after RIT, but it failed to effectively reduce the TSH level. The dose of T4 administered was eventually increased to 250 μg/day at 18 months after the initial examination, but the TSH level remained at 16.92 μIU/mL. Therefore, T4 dosage was reduced to 100 μg/day, and 100 μg/day of liothyronine sodium (T3) was added to the treatment regimen, which successfully reduced the TSH level to 0.004 μIU/mL and Tg level to 67 ng/mL in 6 months.

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Submitted: 15 October 2013

Accepted: 13 December 2013

Published: 17 December 2013

Keywords

- Thyroid stimulating hormone (TSH) suppression
- Thyroxin
- Liothyronine sodium
- Differentiated thyroid carcinoma (DTC)

INTRODUCTION

Thyroid stimulating hormone (TSH) suppression therapy, including the excessive administration of thyroxine (levothyroxine sodium; T4) is commonly initiated after surgical removal of differentiated thyroid carcinoma (DTC) to delay metastasis progression [1-6]. Thyroid hormones consist of 3-mono-iodotyrosine (MIT), 3,5-diiodotyrosine (DIT), T4, triiodothyronin (liothyronine sodium; T3), and reverse T3 (rT3), of which T4, T3, and rT3 are clinically important. Approximately 80% of the T3 produced is formed by the 5′-deiodination of T4 in extrathyroidal tissues. This reaction is catalyzed by type I and type II T4-5′-deiodinases, whose activity is abundant in the liver and kidneys. rT3 is produced at extrathyroidal sites via 5-deiodination of T4 by the enzyme type III T4-5-deiodinase and is widely distributed throughout the body [7-9]. T4 and T3 both possess hormonal activities, but the active strength of T3 is approximately 5 times greater than that of T4 [10,11]. In addition, T4 is believed to be a pre-hormone as it requires conversion to T3 to exert its function, whereas T3 acts directly on organs as a thyroid hormone [10]. The production of the T3 is regulated by TSH, which receives secretory stimulation from thyrotropin-releasing hormone (TRH) secreted by the hypothalamus. Thyroid function is maintained via positive and negative feedback on the hypothalamic-pituitary-thyroid axis [12,13]. In patients with chronic renal failure (CRF), T4 deiodination can be problematic [10,14]. In the present report, we describe a case of CRF and poor TSH control despite sufficient T4 administration for TSH suppression after total thyroidectomy for thyroid cancer.

CASE PRESENTATION

A 37-year-old man had been managed with insulin therapy and modified diet for the treatment of diabetes complicated with diabetic eye disease and nephropathy. He then underwent total thyroidectomy and neck dissection for multiple cervical lymph

Table 1: A blood test at the initial visit.

WBC	7700	4300~8000 / uL
RBC	4.43	4.5~5.1 million / uL
Platelet	136,000	180,000~340,000 / uL
BUN	15	7~18 mg / dL
Cr	1.24	0.5~1.10 mg / dL
Na	142	137 ~146 mEq / L
K	3.9	3.8~5.1 mEq / L
AST	14	13 ~ 33 IU / L
ALT	21	8~42 IU / L
LDH	185	119 ~ 229 IU / L
fT3	2.0	2.6 ~ 4.2 pg / mL
fT4	1.0	0.9 ~1.7 ng / dL
TSH	48.8	0.32 ~ 4.04 μIU / mL
Tg	73.8	0.0 ~ 30 ng / mL

Tg: Thyroglobulin

node (LN) metastases from thyroid cancer. However, residual metastatic lesions were detected, and the patient was referred to our hospital for I-131 radioiodine therapy (RIT). He also received 125 μg/day of T4 orally as TSH suppression therapy. A blood test at his initial visit showed that the fT3 levels were 2.0 (normal range, 2.6–4.2) pg/mL, fT4 levels were 1.0 (0.9–1.7) ng/mL, TSH levels were 48.8 (0.32–4.04) μIU/mL, and thyroglobulin (Tg) levels were 73.8 (0–30) ng/mL. In addition, we observed slightly elevated levels of blood urea nitrogen (BUN) at 15 mg/dL and creatinine (Cr) at 1.24 mg/dL (Table 1). RIT was performed 3 months after the initial examination and abnormal I-131 uptake at the residual mediastinal lymphnode (LN) metastases was detected. The T4 dosage was then increased from 125 μg/day to 150 μg/day after RIT. 3 months after the treatment, the fT4 levels decreased from 1.0 to 0.74 ng/mL, fT3 levels decreased from 2.0 to 1.5 ng/mL, and TSH levels increased from 48.8 to 62.6 μIU/mL (Table 2). At that time, the T4 dosage was believed to be insufficient and was therefore increased from 150 μg/day to 200 μg/day.

Four months after the first dose increase, the serum fT4 level increased to within the normal range at 1.32 ng/mL, while the fT3 level also increased to 2.1 ng/mL, but did not reach the normal range. The TSH level decreased to 14.7 μIU/mL, which was still abnormally high, but the Tg level increased to 76.2 ng/mL (Table 2).

Another RIT was performed after an increase in the number of residual metastatic lesions was confirmed by computed tomography (CT) and the lesions were resected. The dosage of T4 was then increased from 200 μg/day to 250 μg/day upon completion of the second RIT. However, 4 months after the second RIT, the blood fT4 level decreased from 1.32 to 1.27 ng/mL, the fT3 level decreased from 2.1 to 1.57 ng/mL, the TSH level increased from 14.7 to 16.92 μIU/mL and the Tg level increased from 76.2 to 161.3 ng/mL (Table 2).

Although the T4 dosage was increased to 250 μg/day, the fT4 and fT3 levels decreased, compared to the levels at the previous examination. The patient received daily T4 administration consistently until malabsorption of T4 and severe fT3 deficiency were observed. Therefore, we believed that TSH suppression with only T4 administration would not be achievable in the present case. Consequently, T4 dosage was reduced from 250 μg/day to 100 μg/day, while T3 was added to the regimen at 50 μg/day. Four months after the adjustment, the fT4 level decreased from 1.27 to 0.76 ng/mL, but the fT3 level increased from 1.57 to 2.72 ng/mL. The level of TSH remarkably decreased from 16.92 to 0.06 μIU/mL, and the Tg level decreased from 161.3 to 66.9 ng/mL (Table 2). Since the addition of T3 to the regimen seemed to effectively suppress TSH, we continued its administration. After 6 months, a follow-up blood test showed an fT4 level of 0.67 ng/mL, fT3 level of 2.71 ng/mL, TSH level of 0.014 μIU/mL, and Tg level of 67 ng/mL, indicating successful TSH suppression. The BUN level increased to 67 mg/dL and Cr level increased to 4.76 mg/dL (Table 2). During this period, the patient's renal dysfunction was suspected to have progressed rapidly and dialysis was considered, but T3 supplementation was continued.

DISCUSSION

Most DTC patients undergo thyroidectomy, and are thus rendered hypothyroid and require lifetime T4 replacement therapy. An assessment of TSH suppression therapy and the reduction of major adverse clinical events suggested a probable beneficial effect by meta-analysis [4,15]. After 30 years of follow-up, Mazzaferri and Jhiang et al. [16] reported significantly fewer recurrences in patients treated with T4 compared to those receiving no additional therapy ($P < 0.01$). In addition, fewer cancer-related deaths were reported in the T4 group (6% vs. 12%; $P < 0.001$). Landau et al. [17] studied children aged <16 years and found that TSH suppression reduced the tumor recurrence rate ($P = 0.0003$) [4]. Wang et al. [18] showed that during T4 therapy, the mean Tg levels were higher when TSH levels were normal as compared to that when the TSH levels were suppressed; this finding was statistically significant in patients with local or distant relapse ($P = 0.001$). The benefit of TSH suppression therapy is well established in patients considered to be at "high risk." [15,19,20] Several recent guidelines and consensus statements

Table 2: Blood tests and Dosage of Thyroid Hormone.

		At the initial examination		3 months after first RIT		After 4 months		4 months after second RIT		After 4 months		After 6 months
fT3		2.0		1.5		2.1		1.57		2.72		2.71
fT4		1.0		0.74		1.32		1.27		0.76		0.67
TSH		48.8		62.6		14.7		16.92		0.062		0.014
Tg		73.8		22.3		76.2		161.3		54.9		58.8
BUN		15						15				67
Cr		1.24						1.79				4.76
Dosage of T4	125		125 150		200		250		100		100	
Dosage of T3									50		50	

RIT: I-131 radioiodine therapy; fT3: free triiodothyronin; fT4: free thyroxine; TSH: Thyroid stimulating hormone; Tg: thyroglobulin

therefore recommend long-term TSH suppression therapy in such high-risk DTC patients [21,22]. In the present case, the patient was considered to be at "high risk" due to the residual metastases of DTC. TSH suppression therapy with oral T4 at 125 μg/day was initiated but failed to sufficiently increase fT3 and fT4 levels and reduce the TSH level. Despite subsequent increases of T4 dosage to 250 μg/day, the TSH levels decreased from 48.8 to 16.92 μIU/mL, which was not sufficient. The patient's blood test data then showed mal absorption of T4 and fT3 deficiency. One reason for the occurrence of T4 mal absorption could be that the patient consumed T4 orally after breakfast along with other medications. In addition, the fT3 deficiency was believed to result from the dysfunction of deiodination from T4 to T3, which is the main pathway for T3 production after loss of the thyroid glands. Verburg et al. [23] revealed that after long-term (> 3 years) TSH suppression therapy, there are significant changes in thyroid hormone metabolism, which are best explained by a combination of T4-5′-deiodinase downregulation and T4-5-deiodinase upregulation. Moreover, TSH suppression therapy may affect the deiodination of T4 to T3 in the liver and/or kidneys. At the same time, the level of BUN was 15 mg/dL and remained unchanged compared to that at the initial examination while the Cr level increased from 1.24 to 1.78 mg/dL, which suggested exacerbation of the CRF due to diabetic nephropathy. CRF is a relatively common non-thyroidal illness that frequently alters thyroid hormone metabolism. In addition to the metabolic and endocrine instabilities induced by CRF, patients with this condition usually have a multitude of non-renal, non-thyroidal disorders that affect thyroid hormone metabolism, including diabetes mellitus, infection, and malnutrition [14]. As renal dysfunction progresses, deiodination via 5-deiodinase is more effective than deiodination via 5′-deiodinase; therefore, the fT3 level decreases and rT3 level increases in the serum [10,14,23]. At present, the measurement of serum rT3 level cannot be performed in Japan. However, if the increase in the serum rT3 level could be measured, the dysfunction of deiodination from T4 to T3 would be clearly demonstrated. Thus, we believe that, in the clinical practice of TSH suppression therapy, T3 supplementation to the conventional T4 administration should be considered in DIC patients with CRF.

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Cite this article

Kawabe J, Kotani K, Higashiyama S, Yoshida A, Shiomi S, et al. (2013) Challenges in the Suppression of Thyroid Stimulating Hormone in a Thyroid Cancer Patient with Chronic Renal Failure. J Radiol Radiat Ther 2(1): 1021.