

CASE REPORT

A case of resistance to thyroid hormone diagnosed after total thyroidectomy for thyroid cancer

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Abstract : This is a case of a woman who was diagnosed with resistance to thyroid hormone after total thyroidectomy for thyroid cancer. Preoperative laboratory examination revealed the syndrome of inappropriate secretion of TSH, however, the patient had no thyrotoxic symptoms and no family history. Based on the results of ultrasonography and fine needle aspiration, she was diagnosed with papillary thyroid carcinoma and underwent total thyroidectomy. After the surgery, she received L-T4 therapy, but her TSH levels remained elevated. MRI was performed on the brain, but no lesions were found in the pituitary gland. Therefore, she was tested for TR β gene, and a previously defined mutation, P453S, was detected. Ultimately, she was diagnosed as RTH and treated with L-T4. In this case, the dose of L-T4 needed to be increased to suppress her TSH levels to the normal range or less, and to prevent stimulating malignant cells. Currently, her dose of L-T4 has been increased, and her TSH levels are still lower than normal, however, she has no thyrotoxic symptoms, recurrence or metastasis of thyroid cancer. The patient is currently under careful observation regarding her circulatory and physiological status. In addition, the results of treatment still need to be monitored and evaluated. *J. Med. Invest.* 62 : 268-271, August, 2015

Keywords : Resistance to thyroid hormone, papillary carcinoma, total thyroidectomy and levothyroxine therapy

INTRODUCTION

Resistance to thyroid hormone (RTH) is a syndrome involving reduced responsiveness of target tissues to thyroid hormone (TH) (1). Patients with all RTH all have non-suppressed thyroid-stimulating hormone (TSH) levels despite elevated free thyroxine (FT4) and free triiodothyronine (FT3) levels, unless they have a co-existing thyroid disease such as Graves' disease or thyroid autonomy. This condition is known as the syndrome of inappropriate secretion of TSH (SITSH) (2). Patients with TSH-secreting pituitary tumors (TSHoma) and RTH often exhibit SITSH. In majority of patients with RTH, this condition is caused by mutations in the thyroid hormone receptor (TR) β gene (3).

This rare case is an important addition to the literature because there have been few reports on hormone replacement therapy in a patient with RTH and thyroid cancer after total thyroidectomy.

CASE PRESENTATION

A 54-year-old woman was admitted to our hospital because a chest X-ray showed abnormal calcification in the bilateral lobes of the thyroid. She had no typical thyrotoxic signs or symptoms and there was no relevant family history of thyroid disease.

On palpation, her thyroid was mildly enlarged. Electrocardiography showed regular sinus rhythm. On the initial laboratory examination before the operation, thyroid function tests demonstrated slightly elevated values of FT3 and FT4, and TSH was within the normal range. (FT3 6.3 [range, 2.3-4.1] pg/mL, FT4 3.0 [0.7-1.7] ng/dL, TSH 4.03 [0.5-4.3] μ U/mL). Anti-thyroglobulin antibody and anti-thyroid peroxidase antibody were negative, suggesting no

chronic thyroiditis. Thyroglobulin was elevated (90 [0-32.7] ng/mL), thyroid-stimulating antibody and TSH-binding inhibitor immunoglobulin levels were not measured (Table 1).

Table 1. Blood chemistry results

			Normal range
WBC	6.7	$\times 10^3/\mu$ l	4.0-9.5
RBC	4.92	$\times 10^6/\mu$ l	3.5-5.0
Hemoglobin	14.8	g/dl	11.0-15.0
Hematocrit	42.4	%	35.0-45.1
Platelets	20.9	$\times 10^4/\mu$ l	130-400
Ca	9.7	mg/dl	8.0-11.0
P	3.6	mg/dl	2.5-4.5
FT3	6.3	pg/ml	2.3-4.1
FT4	3	ng/dl	0.7-1.7
TSH	4.03	μ U/ml	0.5-4.3
Anti-Tg Ab	10	mg/l	0-40.6
Anti-TPO Ab	1.7	mg/l	0-5.2
Tg	90	ng/ml	0-32.7

WBC : white blood cells, RBC : red blood cells, FT3 : free triiodothyronine, FT4 : free thyroxine, TSH : thyroid-stimulating hormone, anti-Tg Ab : anti-thyroglobulin antibody, anti-TPO Ab : anti-thyroid peroxidase antibody, Tg : thyroglobulin

Ultrasonography showed some masses in the bilateral lobes (one nodule in the right lobe and three nodules in the left lobe). They were hypoechoic and calcified masses, approximately 1 cm in size.

Fine needle aspiration was performed for the nodule with features suggestive of malignancy in the left lobe (Figure 1), and the cytologic diagnosis was papillary carcinoma.

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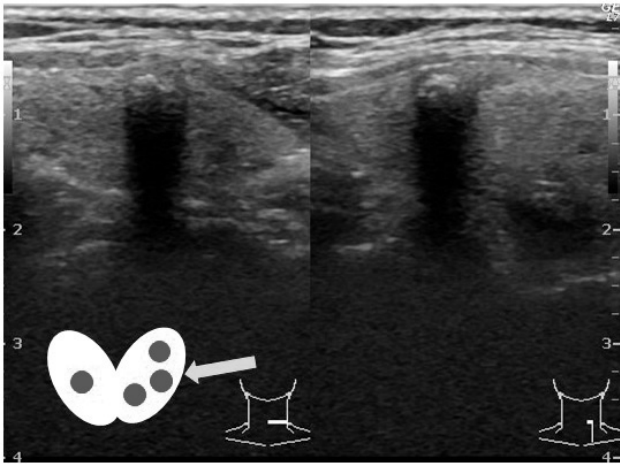


Figure 1. Ultrasonography of the thyroid. Thyroid ultrasonography showed some masses in the bilateral lobes (one nodule in the right lobe and three nodules in the left lobe) suggesting malignancy. Fine needle aspiration was performed for the nodule with features suggestive of a malignancy in the left lobe (arrow).

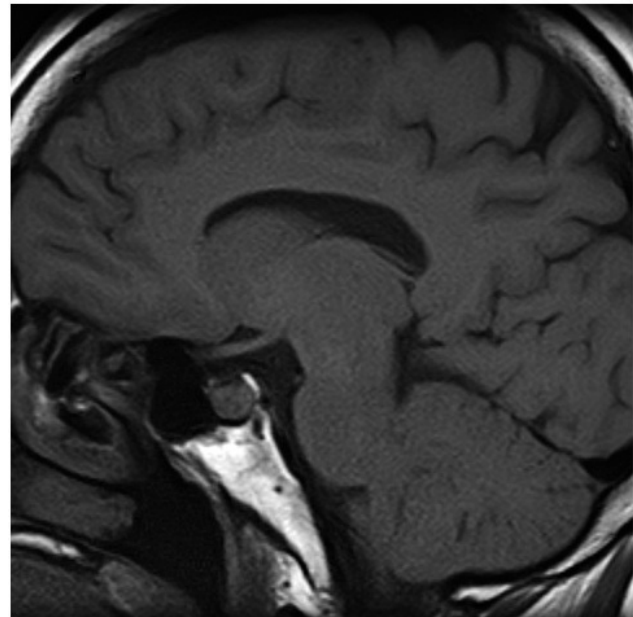


Figure 2. MRI of the brain. No tumors were found in the pituitary gland.

The patient underwent total thyroidectomy and cervical lymph node dissection. Final postoperative pathology revealed four tumors of papillary carcinoma (10 mm×7 mm in the right lobe and 4 mm×4 mm, 10 mm×8 mm, and 4 mm×3 mm in the left lobe), with no metastases to the cervical lymph nodes. On postoperative day 7, she received L-T4 therapy at 100 µg/day. After 1 month of L-T4 therapy, her TSH levels were markedly elevated (FT3 2.9 pg/mL, FT4 1.5 ng/dL, and TSH 103.7 µU/mL). Two months after surgery, the TSH levels were still elevated (FT3 2.7 pg/mL, FT4 1.6 ng/dL, and TSH 102.09 µU/mL). Therefore, the dose of L-T4 was increased from 100 µg to 125 µg daily. Three months post-surgery, the TSH levels were lower (FT3 3.4 pg/mL, FT4 1.8 ng/dL, and TSH 87.45 µU/mL), and the dose of L-T4 was decreased to 100 µg/day. However, 4 months later, the TSH level was elevated again (FT3 2.6 pg/mL, FT4 1.5 ng/dL, and TSH 108.56 µU/mL). The dose of L-T4 was again increased to 125 µg/day, but the TSH levels were not suppressed despite the elevated FT4 (FT3 3.2 pg/mL, FT4 2.1 ng/dL, and TSH 112.59 µU/mL). TSHoma or RTH was then suspected, thus magnetic resonance imaging (MRI) of the brain was performed, but no tumors were found in the pituitary gland (Figure 2), suggesting RTH. Written permission was received from the patient for gene analysis of TRβ as approved by the committee of Tokushima Municipal Hospital. Genomic DNA was isolated from the peripheral blood, and the DNA sequence analysis of the TRβ gene revealed a heterozygous point mutation, CCT to TCT, resulting in substitution of proline by serine at codon 453 (P453S), which has been found previously (Figure 3). Ultimately, she was diagnosed with RTH 7 months after surgery. Gene analysis was recommended to her family, but they declined.

The dose of L-T4 was increased to 350 µg/day. The latest thyroid function tests showed that the TSH level was still slightly suppressed (FT3 6.0 pg/mL, FT4 4.5 ng/dL, and TSH 0.45 µU/mL), and she had no thyrotoxic symptoms (Figure 4). There has been no recurrence or metastasis of thyroid cancer 27 months post surgery.

DISCUSSION

RTH is a syndrome that involves reduced tissue sensitivity to TH (1). Patients with RTH have non-suppressed TSH levels despite elevated FT4 and FT3 levels, unless they have a co-existing thyroid

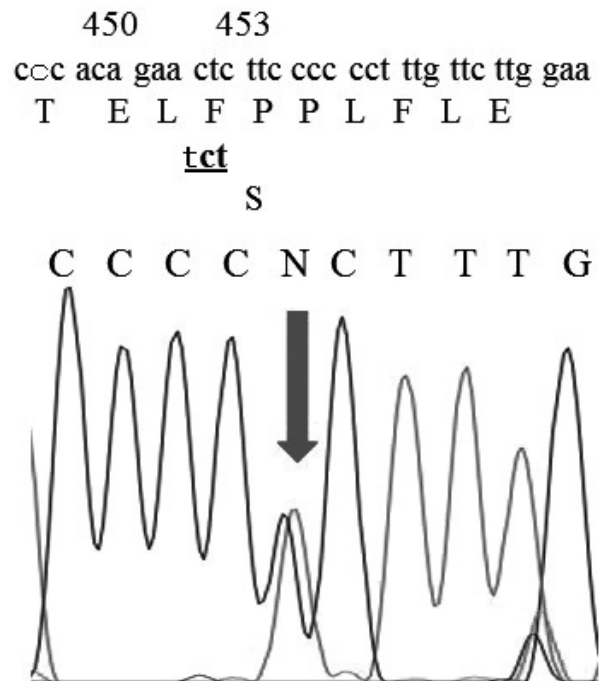


Figure 3. Sequence analysis of the TRβ gene. Sequence analysis of the TRβ gene revealed a heterozygous point mutation, CCT to TCT, resulting in substitution of proline by serine at codon 453 (P453S).

disease such as Graves' disease or thyroid autonomy, this condition is known as SITSH (2). Approximately 85% of RTH kindred cases are caused by mutations in the TRβ gene, which is passed on by autosomal dominant inheritance (3). However, RTH cannot necessarily be ruled out just because there are no mutations in the TRβ gene (4).

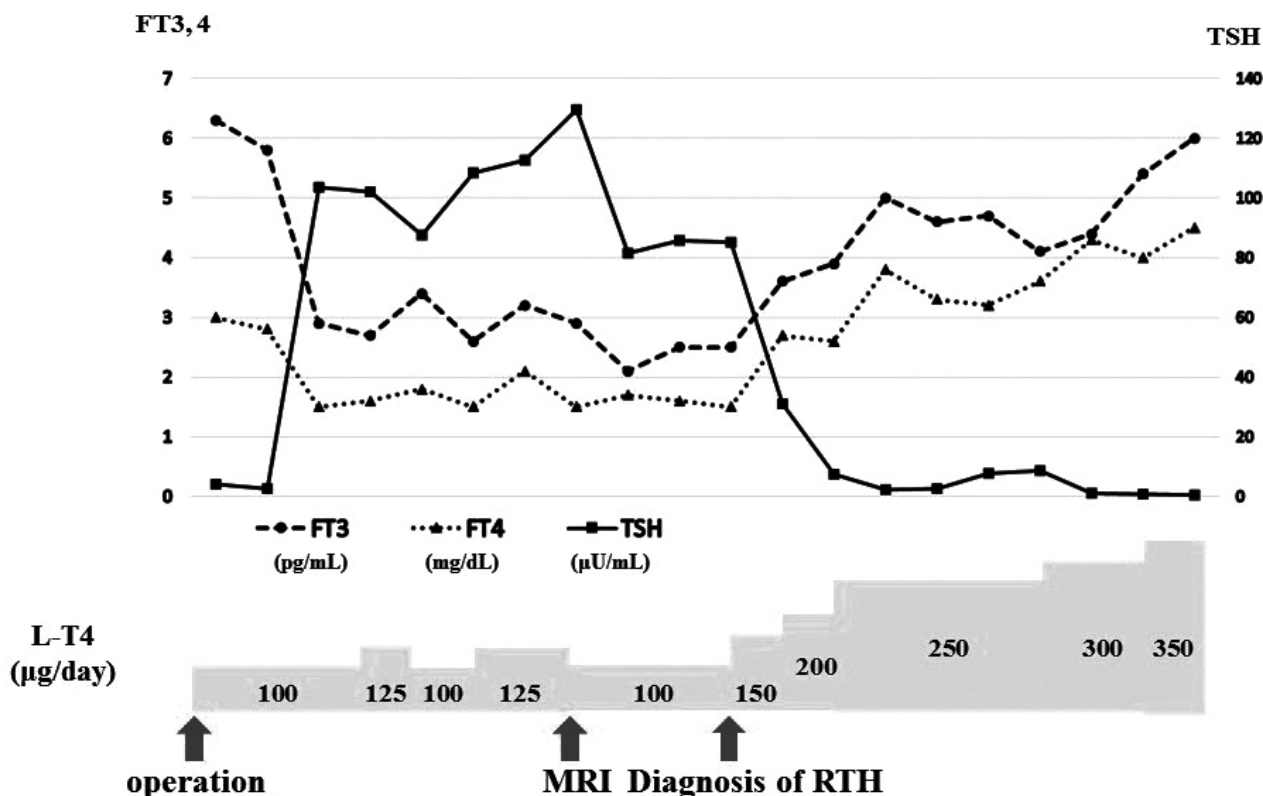


Figure 4. Clinical course of the patient.

L-T4 : levothyroxine

The figure shows the thyroid function tests and the dose of L-T4 after the surgery.

In most patients with RTH, TSH is inappropriately secreted and stimulates the thyroid gland continuously. Thus, such patients' thyroid glands appear mildly enlarged, and iodine¹²³ scintigraphy shows diffuse enlargement of the thyroid gland with increased uptake. Some patients with RTH have thyrotoxic signs and symptoms, such as tachycardia, atrial fibrillation, attention deficit disorder, and hyperactivity (4-7). On laboratory examination, thyroid function tests show unsuppressed TSH levels despite elevated FT4 and FT3 levels (2). In particular, FT4 is elevated in most cases (4, 5).

If thyroid function tests suggest SITSH, assay interference should be excluded, it is occasionally necessary to change the measurement method. If laboratory dates still suggest SITSH, then RTH or TSHoma are suspected, and the patient's family history should first be confirmed. If the patient has no family history of RTH, the next step is to check for a pituitary tumor using MRI to rule out the possibility of TSHoma. In patients with a family history of RTH or those with no lesions in the pituitary gland, analysis of the TR β gene should be performed to confirm a diagnosis of RTH. A diagnosis of RTH can be made if there is a mutation of the TR β gene.

In the present case, the patient's thyroid function tests on initial laboratory examination showed slightly elevated values of FT3 and FT4, with TSH in the normal range. RTH was not suspected at that point, because there was no significant family history or symptoms of hyperthyroidism or hypothyroidism. However, her thyroid function should have been assessed again before the operation. Although the treatment policy was not changed as a result, she may have been able to receive suitable hormone replacement therapy soon after surgery.

Treatment of RTH is unnecessary if the patient has no symptoms. In patients with hypothyroidism, a trial of TH therapy can be considered. If hyperthyroidism is present, β adrenergic blocking agents

and other appropriate agents should be given (4, 6). In the present case, the patient underwent total thyroidectomy for thyroid cancer, and thus required hormone replacement therapy. Two experts (Yoshitaka Hayashi, Associate Professor, and Yoshiharu Murata, former Professor of the Research Institute of Environmental Medicine of Nagoya University) were consulted on how to control the dose of L-T4 in the present case, and they suggested that the patient should have received the appropriate L-T4 dose to achieve the preoperative TSH level. A few cases of RTH with total thyroidectomy have been reported (8, 9), and the TH levels as were controlled in the present case. Moreover, another case report suggested that the family's mean THS level should be used as the target for L-T4 replacement therapy (10). However, this is not available in sporadic RTH patients. Furthermore, the authors of the above study did not evaluate the effect of L-T4 therapy after the operation on the patient's long-term circulatory and physiological status, as well as the prognosis and treatment results of thyroid cancer in such cases.

The method used in the present case appears to be physiologic and suitable as an improved approach to the patient's preoperative condition, although there is no clear evidence to support this. Additionally, I think that estimation of other clinical data, for example, change in body weight, heart rate, creatine kinase, and alkaline phosphatase, would have been useful for evaluating TH level in the patient.

In the present case, it was necessary to increase the dose of L-T4 to suppress the TSH levels to the normal range or less and to prevent stimulating malignant cells based on the general guidelines for thyroid cancer. The patient currently receives 350 μ g/day L-T4 and has no thyrotoxic symptoms. There has been no recurrence or metastasis of thyroid cancer 27 months after the surgery.

In patients with RTH, TSH is unsuppressed. Therefore, the necessary dose of L-T4 will increase if the patient needs hormone replacement therapy, which could cause thyrotoxic symptoms in such patient (4, 5). In addition, there have been a few reports on the long term treatment results of thyroid cancer in such cases. In the present case, the patient will be observed, and the effect of L-T4 therapy will be followed up. Although long-term observation is not possible, I have considered and addressed these issues, and I think that this report provides useful information.

Moreover, my patient had papillary carcinoma. Approximately 95% of RTH patients have diffuse goiter, and continuous stimulation of the thyroid by excess TSH may be related to the formation of thyroid nodules and growth of thyroid cancer (8). However, the contribution of RTH to thyroid tumorigenesis is not fully understood, and there is no confirmatory evidence. Further studies on the association between thyroid cancer and RTH are warranted and I must carefully observe and evaluate my patient for recurrence and metastasis.

CONCLUSIONS

In conclusion, a patient diagnosed with RTH after total thyroidectomy for thyroid cancer was described. It is difficult to decide on the most appropriate dose of TH in these situations and further investigation is required.

LIST OF ABBREVIATIONS

RTH : resistance to thyroid hormone
 TSH : thyroid-stimulating hormone
 SITSH : syndrome of inappropriate secretion of TSH
 FT3 : free triiodothyronine
 FT4 : free thyroxine
 L-T4 : levothyroxine
 MRI : magnetic resonance imaging
 TR : thyroid hormone receptor
 TH : thyroid hormone
 TSHoma : TSH-secreting pituitary tumors

COMPETING INTERESTS

The author declares that he have no competing interests.

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