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Case Report

Development of Thyroid-Stimulating Antibodies and Thyrotoxicosis in a Case of Advanced Follicular Thyroid Carcinoma

Shoko Natsuda[1], Ichiro Horie[1], Takao Ando[1*], Atsushi Kawakami[1]

[1]*Department of Endocrinology and Metabolism, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan*

**Corresponding author: Takao Ando, Department of Endocrinology and Metabolism, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki, 852-8501 Japan, Tel.: +81-95-819-7268; Fax: +81-95-849-7270; Email: takaoando@gmail.com*

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Abstract

It is extremely rare that thyroid cancer produces enough thyroid hormone to cause thyrotoxicosis. We report the case of a 69-year-old Japanese female who developed thyrotoxicosis associated with advanced follicular thyroid carcinoma. The patient had been under levothyroxine replacement therapy for 10 years after a total thyroidectomy, and had undergone radioiodine therapy three times because of multiple lung and bone metastases. She developed thyrotoxicosis at approx. 1 year after external beam radiation therapy against painful bone metastasis. It appeared that excessive thyroid hormones were produced from the metastatic bone tumors, since the thyrotoxicosis continued without levothyroxine replacement, a whole body scan using 123-I was positive in the bone lesions, and the patient was positive for thyroid-stimulating hormone (TSH) receptor antibodies. Her thyrotoxicosis was improved by external beam radiation therapy to the bone lesion that had accumulated 123-I. The appearance of TSH receptor antibodies is one of the causes of thyrotoxicosis seen in patients with thyroid cancer. Our patient's case suggested that tumor cell death as a result of the external beam radiation might have elicited autoimmunity to the TSH receptor autoantigen expressed in the thyroid cancer.

Introduction

Well-differentiated thyroid carcinoma (including follicular thyroid carcinoma and papillary carcinoma) is the major cause of primary thyroid malignancy [1]. It is well known that primary thyroid cancers do not produce enough thyroid hormone to cause thyrotoxicosis in general. However, nearly 80 cases of patients with thyroid cancer who developed thyrotoxicosis with various etiologies have been reported [2-4]. Here we present the case of a Japanese woman with follicular thyroid carcinoma who developed thyrotoxicosis due to thyroid -stimulating antibodies (TSAbs).

Case Report

A 69-year-old Japanese female was admitted to our hospital because of a palpitation in February 2008. She had been under medical treatment for follicular thyroid carcinoma since 1998. When her thyroid cancer was first diagnosed, the thyroid cancer was found to be metastatic to multiple bones and the lungs, and she underwent a total thyroidectomy followed by three courses of radioiodine therapy. She developed a pathological fracture of the right iliac bone in 2005 and was treated with external beam radiation therapy (EBRT). She underwent a second round of radiation therapy for the growing and painful iliac bone lesion in May 2007.

At her admission to our hospital in February 2008, we noted tachycardia (112 beats per min) and swelling of the right hip accompanied by pain on physical examination. There were no thyroid eye signs or pretibial myxedema. Her blood tests indicated the presence of thyrotoxicosis, which had not identified before (Table 1). She was positive for thyrotropin receptor antibodies (TRAbs) (13.4 IU/L, reference range <1.0 IU/L) and TSAbs (570%, reference range <180%). Whole-body scintigraphy showed strong

accumulations of 123-I in the left rib and the right pelvic bone (Figure 1).

Table 1. Appearance of thyrotoxicosis in a patient with levothyroxine supplementation

Date (Y/M)	2007/11	2007/12	2008/1	2008/2	2008/3[1]	2008/3[2]
Free T3 (pg/mL)	3.38	3.82	5.39	10.11	7.77	2.38
Free T4 (ng/dL)	1.27	1.23	1.12	1.42	0.70	0.39
TSH (IU/L)	0.47	0.44	0.008	0.005	0.009	0.006
Tg (ng/mL)	17691	35985	40367	79199	ND	ND
TRAb (IU/L)	0	1.9	4.5	9	13.4	ND
TSAb (%)	106	267	170	570	1052	ND
L-T4 dose (μg/day)	100	100	100	50	None	None

[1] and [2] indicate the blood specimens tested in the May 7th and May 17th, respectively. The reference ranges are 2.30–4.30 for free T3, 0.90–1.70 for free T4, 0.05–5.00 for TSH, and <32.7 for Tg. TSH: thyrotropin, Tg: thyroglobulin, TRAb: thyrotropin receptor antibodies, TSAb: thyroid-stimulating antibodies, L-T4: levothyroxine, ND: not determined.

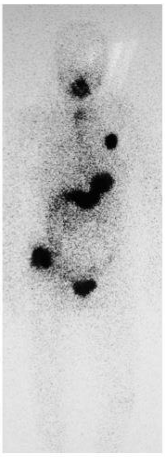

Figure 1. Whole-body evaluation with 123-I in the patient, a 69-year-old Japanese female studied in February 2008. There was a marked accumulation of 123-I in the left rib and the right pelvis.

Even though we discontinued the patient's levothyroxine supplementation, the thyrotoxicosis continued (Table 1), and thus we suspected that her metastatic thyroid cancer was under stimulation of TSAbs causing thyrotoxicosis. We were able to measure TRAbs and TSAbs in some of her sera in the laboratory. The data suggested that the autoantibodies to TSH receptors appeared 1 month before the development of thyrotoxicosis (Table 1).

We administered EBRT against the patient's rib metastasis in order to correct the thyrotoxicosis. The radiation therapy successfully reduced her serum levels of thyroid hormone (free T3 2.38 pg/mL and free T4 0.39 ng/dL), but the patient developed Takotsubo cardiomyopathy and died 1 month after the completion of EBRT.

Discussion

We reported the case of an older female patient with advanced follicular thyroid carcinoma who developed thyrotoxicosis. We concluded that excessive thyroid hormones were produced by the patient's metastatic follicular thyroid carcinoma to the bones. Strong accumulations of 123-I in the left rib and the right pelvic bone in whole-body scintigraphy suggested that these lesions were under stimulation of TSAbs. The thyrotoxicosis improved after external radiation to the metastatic bone tumor.

Several clinical settings can cause thyrotoxicosis in the course of thyroid cancer, seen mostly in patients with follicular thyroid carcinoma [5]. Some patients with follicular thyroid cancer have been shown to convert exogenous levothyroxine to T3 [6,7]. Thyrotoxicosis may be caused by coincidental struma ovarii, which may contain thyrocytes [8].

Autonantibodies to the TSH receptor, TSAbs and TRAbs, are a well-known cause of the autoimmune hyperthyroidism seen in Graves' disease [9] and are also known to cause thyrotoxicosis in patients with thyroid cancer with massive metastasis (10). TSAbs and/or TRAbs may be positive in up to one-fourth of patients with thyroid cancer who show thyrotoxicosis [10]. We also observed the appearance of TSAbs and TRAbs in the present patient, shortly before the development of thyrotoxicosis.

It is not surprising for patients with preexisting Graves' disease to develop thyrotoxicosis from a metastatic thyroid carcinoma after total thyroidectomy, since these patients would remain positive for TSAbs and/or TRAbs [11]. However, during our patient's course, TSAbs and TRAbs were originally negative and eventually became positive. Similar cases have been reported [10,12-15]; some became positive for TSAbs and/or TRAbs after radioiodine therapy [10,12,14] and others after external radiation [13].

There seems to be a possible association between the appearance of TSAbs/TRAbs and radiation-induced damages of thyroid tissues. The appearance of TSAbs/TRAbs has also been reported in patients with nodular toxic goiter after radioiodine therapy [16]. Since thyroid cancer has been shown to express several autoantigens [17], the tissue damage including radioiodine therapy and EBRT, might expose thyroid autoantigens (including TSH receptor) to the immune system and provoke autoimmunity [18].

Radioiodine would be the first choice of treatment in cases of advanced thyroid cancer showing thyrotoxicosis caused by TSAbs/TRAbs, considering a robust uptake of radioiodine in the metastatic lesion(s) producing thyroid hormone [10,12,13]. Another option would be external radiation, as shown in our case. The tumor reduction achieved by using these treatments has shown to improve thyrotoxicosis and to reduce the level of TRAbs and TSAbs [10,12,13].

In summary, we have reported the case of a patient with advanced follicular thyroid cancer. Our case exhibited thyrotoxicosis which was induced by autoantibodies to TSH receptor. Her case suggested that external radiation seemed to have triggered an autoimmune response to TSH receptor expressed in the follicular cancer cells [10].

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