Hypothyroidism Preceding Hyperthyroidism in a Patient with Continuously Positive Thyroid Stimulating Antibody

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A 62-year-old woman was initially hypothyroid and then developed hyperthyroidism with continuously positive thyroid-stimulating antibody (TSAb). When she visited our hospital with the complaint of the feel of skipping beats, her serum free T_4 level was initially low and thyrotropin (TSH) level was slightly elevated. One month after starting the supplement therapy with l- T_4 , she developed hyperthyroidism with increased ^{123}I -thyroid uptake. TSH-binding inhibitor immunoglobulin (TBII) was slightly elevated only during the hypothyroid stage. Throughout the whole course, TSAb was continuously positive, while thyroid stimulation-blocking antibody (TSBAb) was not detectable. Primary hypothyroidism with TSAb may suggest the possibility of subsequent development of hyperthyroidism.

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Key words: thyrotropin binding inhibitor immunoglobulin (TBII), thyroid-stimulation blocking antibody (TSBAb), TSH receptor antibody (TRAb), hypothyroidism, hyperthyroidism

Introduction

It is known that some patients with primary hypothyroidism develop hyperthyroidism. However, there have been few studies in which thyrotropin (TSH) receptor antibody (TRAb) was serially determined during the course of the illness from hypothyroidism to hyperthyroidism (1–8). The sequential change in TRAb was observed also in euthyroid subjects who subsequently developed hyperthyroidism due to Graves' disease (9–11). Here we report a case of mild primary hypothyroidism with moderately positive thyroid-stimulating antibody (TSAb) two months before the onset of Graves' hyperthyroidism.

Methods

TSH-binding inhibitor immunoglobulin (TBII), TSAb and thyroid-stimulation blocking antibody (TSBAb) were measured by the following methods. TBII was measured by a radioreceptor assay for TSH (12) (normal <15%). TSAb was determined by a bioassay which measures cyclic adenosine monophosphate (cAMP) produced in cultured porcine thyroid cells as an index of stimulation according to the method developed by Amino et al (13) and Watanabe et al (14). Briefly, the thyroid cell suspension was incubated with crude IgG fractions sedimented by 15% polyethylene glycol in hypotonic

medium. The amount of cAMP released during the 18-hour incubation was determined, and the potency of TSAb was expressed as an equivalent of bTSH [normal, <0.3 $\mu\text{U}/\text{ml}$ bovine TSH equivalent (bTSH eq.)]. In this assay system, bTSH at 1, 10 and 100 $\mu\text{U}/\text{ml}$ elicits a 3.6-, 14.6- and 43.0-fold increase in cAMP, respectively. To determine the activity of TSBAb, the thyroid suspension was incubated with the crude IgG fraction and bTSH (the final concentration, 100 $\mu\text{U}/\text{ml}$) for 2 hours. The blocking activity was expressed as the percentage inhibition of cAMP increase, calculated as follows: $[1 - (\text{cAMP generated in the presence of patient's IgG and TSH} / \text{cAMP generated in the presence of normal pooled IgG and TSH})] \times 100\%$ (normal <20%). Serum TSH at concentrations lower than 30 $\mu\text{U}/\text{ml}$ does not cause false-positive or false-negative results from these TSAb and TSBAb measurements, respectively (15).

Case Report

A 62-year-old woman visited to our hospital in August 1992 due to the feeling of skipping beats and general fatigue. She had a decreased pulse rate, a small goiter without any tenderness, and no exophthalmos. Her goiter had been pointed out in June 1992 at a general clinic but she had been given no medicine. She had had no iodine overintake. Serum free T_4 , total T_3 and TSH levels were 0.46 ng/dl, 102 ng/dl, 19.6 $\mu\text{U}/\text{ml}$, respectively.

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One month after treatment with l-T₄ (50 µg/day), she developed tachycardia and moist skin. Serum free T₄ and total T₃ levels were 9.91 ng/dl and 484 ng/dl, respectively. The serum TSH level was undetectably low on October 13 while taking 50 µg/day l-T₄. The titers of autoantibodies against thyroglobulin (TGHA) and microsomes (MCHA) were $\times 200$ and $\times 3,200$, respectively. Seven days following discontinuation of the l-T₄ therapy on October 20, she still showed signs of overt hyperthyroidism; methimazole treatment was then started. Ultrasonography of the thyroid performed on October 13 revealed diffuse enlargement with normal echogenicity. ¹²³I-thyroid uptake 3 hours after oral administration of 3.7 MBq Na ¹²³I was increased (15.9%; normal range 5–14%) with diffuse but slightly uneven distribution of the radionuclide (Fig. 1). After discontinuation of methimazole treatment on October 30, methimazole was started again on November 21 because of hyperthyroidism. She remained euthyroid both clinically and biochemically under methimazole treatment from August 13, 1993 until the latest follow-up date (March 1994).

As shown in Table 1, TBII and TSAb activities were positive at 18.3% and 2.8 µU/ml bTSH eq, respectively, in the hypothyroid state when she was first seen at our hospital in August 1992. When she became hyperthyroid in October 1992, TBII became undetectable. Since then TBII has been negative. TSAb and TSBAb activities have remained positive and negative, respectively, throughout the observation period.

Discussion

The thyrotoxicosis observed in the present patient can be explained by hyperthyroidism due to Graves' disease because of the detection of TSAb in her serum and the increased ¹²³I thyroidal uptake. Three factors are considered to be responsible for the change in her thyroid function from hypothyroidism to hyperthyroidism: 1) disappearance or decrease in titer of a blocking-type TRAb (2–4, 6–8), 2) emergence or increase in titer of stimulating-type TRAb (1–5, 7, 8), and 3) recovery from transient hypothyroidism concomitant with hyperthyroidism (16).

The present assay for TSBAb yields underestimation of the activity in serum samples with positive TSAb, since the production of cAMP in the presence of TSAb-positive IgG and TSH is greater than that in the presence of control IgG and TSH. This could raise the possibility that her hypothyroidism might have been due to the inhibitory effect of blocking TRAb on the thyroid function. According to Konishi et al (17), TSBAb activities are detected in hypothyroid patients with weakly positive or even in those with negative TBII. Detection of TBII only in the hypothyroid state might suggest the blocking nature of the antibody. However, it is unlikely that the present patient had a blocking TRAb and showed false-negative activity of TSBAb, in view of the cAMP responses to 100 µU/ml bTSH

Fig. 1. Scintigraphic appearance of the thyroid gland. Scanning with ¹²³I was performed on November 5, 1992. ¹²³I-thyroid uptake three hours after oral administration of 3.7 MBq Na ¹²³I was 15.9% (the normal range, 5–14%).

Table 1. Thyroid Function Tests, TSH Receptor Antibodies and Treatment Regimen during the Observation Period

	FT ₄ (ng/dl)	T ₃ (ng/dl)	TSH (µU/ml)	TGHA	MCHA	TBII (%)	TSAb (µU/ml bTSH eq)	TSBAb (%)	Treatment
24 Aug. 1992	0.46	102	19.6	N.D.	N.D.	18.3	2.8	–18.9	–
13 Oct. 1992	9.91	484	<0.05	$\times 200$	$\times 3,200$	N.D.	N.D.	N.D.	l-T ₄ 50µg/D
27 Oct. 1992	3.42	214	<0.05	$\times 100$	$\times 3,200$	9.3	0.4	–10.4	MMI 15mg/D
16 Nov. 1992	3.59	171	<0.05	$\times 100$	$\times 3,200$	11.3	2.0	–1.1	–
7 Dec. 1992	3.20	189	<0.05	$\times 100$	$\times 6,400$	9.1	5.0	–15.5	MMI 15mg/D
28 Dec. 1992	2.03	143	<0.05	$\times 100$	$\times 3,200$	N.D.	1.0	–13.3	MMI 15mg/D
17 Aug. 1993	0.74	129	4.47	$\times 200$	$\times 1,600$	2.9	0.5	N.D.	MMI 15mg/D
7 Dec. 1993	0.90	126	3.29	N.D.	N.D.	5.7	N.D.	N.D.	MMI 5mg/D
1 Mar. 1994	0.91	118	2.70	N.D.	N.D.	0.0	N.D.	N.D.	MMI 5mg/D
Normal range	0.8–1.8	93–181	0.34–3.5	<100	<100	<15	<0.3	–29~+21	

Duration of l-T₄ treatment: from September 21 to October 13. Duration of MMI treatment: from October 20 to October 30, and from November 21 to the latest follow-up date. N.D.: not determined, D: day.

employed for the TSAb assay (43-fold increase) and to the patient's IgG in the TSAb assay (9.2-fold increase) and the assay result from TSAb measurement (−18.9% in Table 1).

Diffuse but slightly patchy uptake of ^{123}I suggests that the present patient had concomitant Hashimoto's thyroiditis. Therefore, it is conceivable that thyroid follicular cells with severe autoimmune destruction might have caused hypothyroidism in spite of the presence of TSAb, and that the balance between the stimulatory effect of TSAb and the thyroid destruction was altered to cause subsequent hyperthyroidism. However, there was no increase in TSAb activity in concurrence with the development of hyperthyroidism, unlike most patients with the early stage of Graves' disease (10). TSAb in her serum fluctuated but was continuously positive throughout the whole course. The slight decrease in TSAb on October 27, 1992 might have been reflective of the natural course of the disease (18, 19) and/or the secondary suppression of TSH after T_4 administration (19–21).

With respect to the third factor responsible for the change of her thyroid function, transient hypothyroidism induced by an iodide overintake has been reported in a TSAb-positive patient with subclinical hyperthyroidism (22). However, the present patient did not take excessive iodine.

Shigemasa et al (16) recently reported a case of transient hypothyroidism following subacute aggravation of chronic thyroiditis during antithyroid drug therapy for Graves' hyperthyroidism. Although the past history revealed that the present patient had not presented thyrotoxic symptoms, we would speculate that she was in the hypothyroid state at her first visit following destructive thyroiditis. It is uncertain whether the development of hypothyroidism was preceded by the detection of TSAb or not. In this regard, Morita et al (23) and Tamai et al (24) reported that TSAb and TBII are detected in some patients with silent thyroiditis and subacute thyroiditis, respectively, suggesting that the tissue damage due to destructive thyroiditis causes a release of antigen and a corresponding increase in TBII and TSAb activities.

There may be other unknown factors involved in the mechanism of impaired responses of thyroid follicular cells to TSAb at the hypothyroid phase. The possibility that the abnormal response of the PIP_2 cascade, an alternative index of thyroid stimulation for TSH and TRAb, was somehow changed could also be considered.

Although the detection of TSAb in autoimmune hypothyroidism has been reported to be uncommon (1, 4–7, 22, 18–20, 25–31), it is important to keep in mind that hypothyroid patients with positive TSAb may quickly develop Graves' hyperthyroidism as discussed in previous reports (1, 4–7, 22) and in the present paper.

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