Induction of Autoimmune Hypothyroidism and Subsequent Hyperthyroidism by TSH Receptor Antibodies following Subacute Thyroiditis: A Case Report

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Abstract. A 45 year-old man had a typical episode of subacute thyroiditis with tender goiter, depressed radioiodine uptake (RAIU) and elevated erythrocyte sedimentation rate. The titer of TSH binding inhibitor immunoglobulin (TBII), which had been 8.6% at initial presentation, rose to 14.9% in 2 weeks. TBII consisted of high titers (94%) of TSH stimulation-blocking antibodies (TBAb) and negative thyroid stimulating antibodies (TSAb). About 2 months after the first visit, TBII titers had risen to 48.9% and were persistently elevated for 5 months with high TBAb activity. The patient developed hypothyroidism with a maximum serum TSH level of 54.5 μU/ml. TBII and TBAb titers then gradually decreased, and the patient spontaneously recovered from hypothyroidism. Eighteen months after the episode of subacute thyroiditis, he became hyperthyroid with elevated TSAb and negative TBAb values. Doppler ultrasonography showed increased blood flow in the thyroid, and RAIU at 24 h was 53%. He was treated with antithyroid drugs, and soon became euthyroid. This case indicates that subacute thyroiditis can induce thyroid autoimmunity, and that the character of TSH receptor antibodies (TSHRAb) in these patients can change thereby modifying their thyroid function.

Key words: Subacute thyroiditis, TSH receptor antibody, Autoimmune thyroid disease

We have reported the development of TSH receptor antibody (TSHRAb)-associated thyroid dysfunction following subacute thyroiditis [1]. We demonstrated that TSH binding inhibitor immunoglobulin (TBII), which inhibits the binding of labeled TSH to the TSH receptors, became positive in 38 out of 1697 (2.2%) patients with subacute thyroiditis. Thyroid function after the development of TBII appeared to be influenced by the bioactivity of TSHRAbs including stimulating antibodies (TSAb), blocking antibodies (TBAb), and apparently nonfunctioning antibodies. TSAb stimulate thyroid cells to produce adenosine 3',5'-monophosphate (cAMP) [2], and TBAb inhibit TSH-induced cAMP increase [3]. In our previous study, we divided TSHRAb-associated thyroid dysfunction following subacute thyroiditis into 5 categories. Patients with type 1, including types 1a, 1b, and 1c, become positive for TBII within 3 months after the onset of subacute thyroiditis. Patients with types 1a, 1b, and 1c have TSAb, TBAb, and apparently nonfunctioning TSHRAb, respectively. They become hyperthyroid, hypothyroid, and euthyroid, respectively. Those with type 2, including types 2a and 2c, are negative for TBII in the acute phase, but become positive more than 3 months after the onset of subacute thyroiditis. Patients with type 2a develop hyperthyroidism, while those with type 2c have normal thyroid function.

In this report, we describe a patient who became hypothyroid with high TBAb followed by hyper-
thyroidism with positive TSAb. This patient had characteristics of both type 1b (blocking type) and type 2a (stimulation type) thyroid dysfunction caused by TSHRAb following subacute thyroiditis.

**Subject and Methods**

**Laboratory measurements**

Serum FT$_4$, FT$_3$, and TSH were measured using commercially available kits (Amerlex MAB FT$_4$ and FT$_3$, Ortho-Clinical Diagnostics, Tokyo, Japan; Riagnost hTSH, Behring Co., Marburg, Germany). TBII, anti-thyroglobulin antibody (TgAb), and anti-thyroid peroxidase antibody (TPOAb) were determined employing kits from Cosmic Corporation (Tokyo, Japan). TSAb and TBAb were measured using commercially available bioassay kits with porcine thyroid cells from Yamasa Shoyu Co. (Tokyo, Japan) [2, 3].

**Case report**

A 45 year-old man presented with fever and neck pain at our hospital in October 1996. The thyroid, especially the right lobe, was enlarged with severe spontaneous pain and tenderness. He had been healthy except for an appendectomy in September 1970. His mother had primary biliary cirrhosis, and a maternal aunt had Graves' disease. His laboratory data were compatible with subacute thyroiditis. The erythrocyte sedimentation rate was 130 mm/1h, and CRP 12.7 µg/ml. Serum FT$_4$, FT$_3$, and TSH concentrations were 4.92 ng/dl (reference range: 0.8~1.8), 15.8 pg/ml (reference range: 2.6~4.8), and <0.1 µU/ml (reference range: 0.3~4.0), respectively. Serum thyroglobulin concentrations and titers of TgAb and TPOAb were 600 ng/ml (reference range: <30), <0.3 U/ml , and <0.3 U/ml, respectively. TBII was 8.6% (reference range: 10~20), and radioactive iodine uptake (RAIU) at 24 h was 3.1%. Ultrasonography showed an enlargement of the right lobe and an irregular hypoechoic lesion in the thyroid. No blood flow was detected in the thyroid by color doppler ultrasonography. Administration of prednisolone was initiated.

Two weeks after his first visit, serum FT$_4$ and FT$_3$ levels were normalized (1.38 ng/dl and 3.9 pg/ml, respectively), but TBII became weakly positive (14.9%). TSAb was normal (92%; reference range <180), but TBAb was strongly positive (94%; reference range <40%). In December, TBII rose to 48.9%, and serum FT$_4$, FT$_3$, and TSH levels were 1.04 ng/dl, 2.5 pg/ml, and <0.1 µU/ml, respectively. In January, 1997, his serum FT$_4$, FT$_3$, and TSH levels were 0.25 ng/dl, 1.6 pg/ml, and 32.7 µU/ml, respectively. TBII, TSAb and TBAb were 51.4%, 120% and 97%, respectively. No treatment was given as he was asymptomatic. In March, his serum FT$_4$, FT$_3$, TSH, and TBII levels were 0.58 ng/dl, 2.8 pg/ml, 54.4 µU/ml, and 49.1%, respectively. In May, his serum FT$_4$, FT$_3$, TSH, and TBII levels were 1.10 ng/dl, 3.3 pg/ml, 9.0 µU/ml, and 39.1%, respectively. TSAb and TBAb levels were 131% and 95%, respectively. Ultrasound examination showed a slightly atrophic thyroid gland with approximate volume of 9.8 cm$^3$. In October, his thyroid function was almost normal with serum FT$_4$, FT$_3$, and TSH levels of 1.16 ng/dl, 3.5 pg/ml, and 4.6 µU/ml, respectively, although TBII (31.8%) and TBAb (72%) levels were still high. He then stopped visiting our hospital, but his thyroid function was normal according to measurements done at another institution in December.

Although he was asymptomatic, his thyroid hormone levels increased in April, 1998. Serum FT$_4$, FT$_3$, TSH, TBII, TSAb, and TBAb levels were 1.68 ng/dl, 6.68 pg/ml, <0.01 µU/ml, 17.5%, 252%, and <1%, respectively. RAIU at 24 h was 53%, and Doppler ultrasonography showed some blood flow in the thyroid parenchyma. He was treated with 5 mg of methimazole. After taking methimazole for 1 month, serum ALT, AST, and γ-GTP increased. Methimazole was then stopped, and Lugol's solution was administered for 2 months. As serum transaminases returned to normal, 50 mg of propylthiouracil was started. His thyroid functions were normal in July; serum FT$_4$, FT$_3$, TSH, TBII, TSAb, and TBAb levels were 1.40 ng/dl, 3.7 pg/ml, 1.92 µU/ml, 17.7%, 292%, and 18%, respectively. Neither TgAb nor TPOAb were positive throughout the course. No pretibial myxedema or ophthalmopathy was observed. He is still taking 50 mg of propylthiouracil daily because TSAb levels remain high. The clinical course is shown in Fig. 1.
Discussion

According to our recent report on the development of TSHRAb following subacute thyroiditis [1], this case can be classified as type 1b plus type 2a. This is the first case in our experience who sequentially developed TBAb-positive hypothyroidism followed by TSAb-positive hyperthyroidism after an episode of subacute thyroiditis. TBII had been negative initially but became positive within a month after the onset of subacute thyroiditis. This is characteristic of type 1b patients. In this case, TBII was the blocking type TSHRAb (TBAb) that persisted for 1 year, and stimulating type TSHRAb (TSAb) was not detected. His serum TSH levels persistently elevated for about 1 year, indicating that TBAb actually suppressed his thyroid function in vivo. Since the patient was asymptomatic, and our previous study showed that most type 1b patients recover from hypothyroidism spontaneously, he was left untreated. He did, as expected, recover spontaneously, but then unexpectedly developed hyperthyroidism. In our previous study, no type 1b patient later developed hyperthyroidism.

Development of hyperthyroidism and the alteration from TBAb to TSAb occurred 18 months after the onset of subacute thyroiditis in this case. In our previous study, TSHRAb developed 5 months to 4 years after the onset of subacute thyroiditis in type 2a patients. We previously found that some type 2a patients had both TSAb and TBAb simultaneously. In this case, the character of TSHRAb appears to have changed abruptly. Development of TBAb about 1 month after subacute thyroiditis indicates that B cells which produce TBAb and/or T cells sensitized with a specific antigen were already primed before subacute thyroiditis. On the other hand, T cells sensitized to the epitope for TSAb and B cells producing TSAb were apparently primed after subacute thyroiditis. It appears that the immune surveillance system successfully suppressed the preexisting TBAb-secreting B cells first. Then, the predominant TSAb-secreting B cells produced TSAb leading to autoimmune hyperthyroidism.

Several reports have described the development of autoimmune hyperthyroidism following primary hypothyroidism [4-8]. In these reports, patients developed hyperthyroidism 1 to 20 years after the diagnosis of primary hypothyroidism. Two patients were reported to have TSAb in the hyperthyroid phase and TBAb in the hypothyroid phase. Recent studies have shown that patients with autoimmune thyroid disease can produce different types of TSHRAbs which recognize different epitopes of the TSH receptors [9, 10]. These TSHRAbs can modify the patients' thyroid functions, resulting in hyperthyroidism or hypothyroidism. The major difference between our case and previously reported cases is that our patient had typical subacute thyroiditis which appears to trigger subsequent autoantibody production.

In this patient, the family histories of Graves' disease and primary biliary cirrhosis suggest that he may have had a genetic background predisposing to autoimmune diseases. In our previous study, a significantly higher prevalence of family history of thyroid disease was observed in patients who became positive for TSHRAb after subacute thyroiditis [1]. Thus antigenic release in response to inflammation may affect the immune surveillance system in apparently normal persons who have a genetic background.
predisposing them to autoimmune disease, resulting in autoantibody production. The production of autoantibodies may be transient, probably because the immune surveillance system once damaged by an antigenic challenge may recover with time and suppress autoantibody production in these patients. This case, in addition to our previous study, shows that subacute thyroiditis can induce autoimmune thyroid dysfunction even in apparently healthy people, and that the character of TSHRAb may change with time. Thyroid function in these patients can be influenced by the stimulating or inhibitory activity of TSHRAb.

References


