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【 CASE REPORT 】

Painless Thyroiditis with Thyrotropin Receptor-blocking and Receptor-stimulating Autoantibodies

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Abstract:
We herein report a rare case of a 41-year-old woman with painless thyroiditis who was positive for thyrotropin (TSH) receptor-blocking (TBAbs) and receptor-stimulating autoantibodies (TSAbs) in the thyrotoxic phase. Her serum thyroid hormone levels were high, and TSH was undetectable. The low uptake of ^{99m}Tc led to the diagnosis of painless thyroiditis. M22-TRAb, TBAb and TSAb were detectable in the thyrotoxic phase. Three months later, she became severely hypothyroid. M22-TRAb and TBAb were still strongly positive, although the TSAb levels had decreased to just above the reference range. In this case, TBAb led to hypothyroidism.

Key words: painless thyroiditis, M22-TRAb, TBAb, TSAb

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Introduction

Painless thyroiditis is a well-known disease, characterized by transient thyrotoxicosis, a non-tender thyroid gland, and a low radioactive iodine or ^{99m}Tc uptake (1). Among patients with painless thyroiditis, 60.7% developed hypothyroidism after transient thyrotoxicosis. While hypothyroidism spontaneously resolves in the majority of cases, permanent hypothyroidism occurs in 5.4% (2).

Painless thyroiditis is subclassified into sporadic type, which includes thyroiditis unrelated to pregnancy, postpartum thyroiditis and gestational painless thyroiditis (2); exogenous painless thyroiditis (3); and "others," including that induced by neck radiation, trauma and post-^{131}I therapy for Graves' disease (GD) (3). The discrimination of GD and painless thyroiditis is important, as each disease demands a completely different therapy. GD is treated by antithyroid drugs and radioactive iodine, whereas painless thyroiditis resolves spontaneously. The assessment of thyrotropin receptor autoantibody (TRAb), which causes hyperthyroidism in GD, is a useful marker for distinguishing between GD and painless thyroiditis (1).

To our knowledge, this is the first reported case of painless thyroiditis that was positive for M22-TRAb, TSH receptor-blocking antibody (TBAb) and TSH receptor-stimulating antibody (TSAb) during the thyrotoxic phase.

Assays

Free thyroxine (FT4), free triiodothyronine (FT3), thyrotropin (TSH), thyroperoxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) levels were measured with an electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). The reference limits of FT4, FT3 and TSH were 0.80-1.90 ng/dL, 2.00-4.40 pg/mL and 0.45-4.50 μU/mL, respectively. Positive thyroid autoantibodies were defined as a TPOAb concentration of >52 IU/mL and/or TgAb >40 IU/mL, as calculated from the receiver operating characteristic (ROC) analysis using patients' serum samples collected before the operation for thyroid tumors (mainly papillary cancer), as previously reported (4).

M22-TRAb assay

The M22-TRAb levels were measured by an inhibition assay kit-Elecsys anti-TSH receptor assay (Roche Diagnostic) according to the manufacturer's instructions (1). This assay detects M22-TRAb via the inhibition of a monoclonal anti-

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Table. Findings for the Thyroid Function Tests, TSH Receptor Autoantibodies and Treatment Regimen in the Patient during the Observation Period.

Year/Months	FT3 (pg/mL)	FT4 (ng/dL)	TSH (μU/mL)	M22-TRAb (IU/L)	TBAb (%)	TSAb (%)	TgAb (IU/mL)	TPOAb (IU/mL)	LT4 (μg/day)
Reference range	2.00-4.40	0.80-1.90	0.45-4.50	2.0	<34	120	<40	<52	
2018/12	5.34	1.92	<0.01	16.8	98.4	215	378.0	10.2	
2019/01	3.24	1.35	<0.01	25.3	100.7	163	431.1	8.7	
2019/03	0.85	0.24	118.6	26.4	98.9	129	382.6	11.7	75
2019/04	2.65	1.41	13.2	24.2		122	319.7	14.7	75

FT3: free triiodothyronine, FT4: free thyroxine, TSH: thyrotropin, M22-TRAb: M22-thyroid receptor autoantibody, TBAb: thyroropin receptor-bloking autoantibodies, TSAb: thyrotropin receptor-stimulating autoantibody, TgAb: thyroglobulin antibody, TPOAb: thyroperoxidase antibody, LT4: levothyroxine

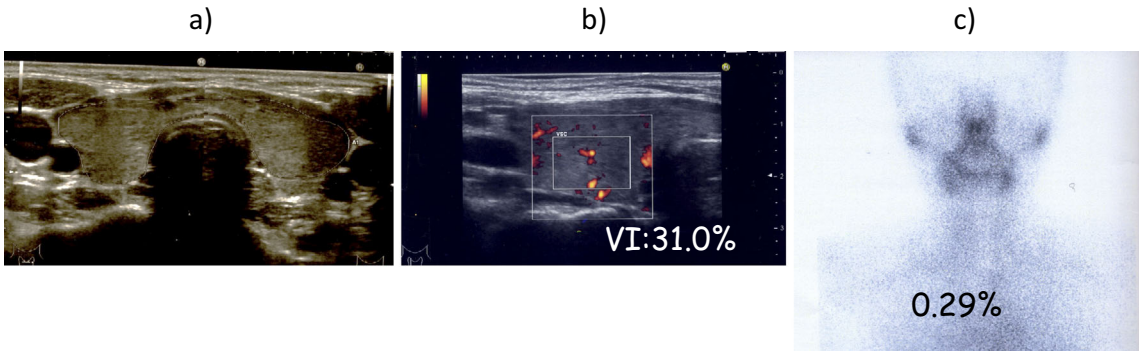

Figure. An ultrasound of (a) B-mode and (b) color Doppler (power mode) and (c) a thyroid scan with ^{99m}Tc.

body (M22) binding the extracellular domain of porcine TSHR. The estimated optimal M22-TRAb cut-off value was 2.0 IU/L (5). The intra- and inter-assay coefficient of variations (CVs) for M22-TRAb in 4 different serum samples ranged from 0.8-9.4% and 1.3-22.0% (1), respectively.

TSAb and TBAb assays

Using a porcine thyroid cell cAMP system, TSAb levels were measured with a TSAb kit [YAMASA] EIA bioassay according to the manufacturer's instructions (Yamasa, Chiba, Japan), as previously described (6). This bioassay specifically stimulates TSAb activation via the expression of the wild-type receptor on cultured porcine cells. Binding of TSAb in the patient sera to the TSH receptor on porcine thyroid cells leads to adenyl cyclase activation, which increases the release of intracellular cAMP into the culture medium. After cell lysis with TritonX100, the total cAMP inside the porcine thyroid cells and in the culture medium is measured by a solid phase enzyme immunoassay, for a total assay time of one hour. The estimated cut-off value of TSAb was 120%. The intra- and inter-assay CVs in 3 different serum samples ranged from 3.2-5.9% and 3.7-5.6% (6), respectively.

Using the same porcine thyroid cell cAMP system, the TBAb activity was assayed by measuring the ability of patients' sera to prevent bovine TSH (bTSH) from stimulating cAMP production in comparison to the control serum response, as previously described in detail (7). The estimated cut-off value of TBAb was 34%. The intra- and inter-assay CVs in 4 different serum samples ranged from 1.2-7.4% and 1.3-5.5%, respectively.

Case Report

A 41-year-old woman first visited our clinic in December 2018 with mild complaints of thyrotoxicosis, including irregular menstruation, palpitation, short breath and perspiration without hand tremor and weight change. No goiter was palpable. She had no history of thyroid disease or drug consumption.

The results of thyroid function tests at the initial visit are shown in Table. The serum levels of FT3, FT4 and TSH were 5.34 pg/mL, 1.92 ng/dL and <0.01 μU/mL, respectively. TgAb was positive (378.0 IU/mL), and TPOAb was undetectable. M22-TRAb (16.8 IU/L) and TBAb (98.4%) were strongly positive, and TSAb (EIA) was mildly elevated to 215%. An ultrasound revealed a normal-sized thyroid gland [22 g (reference range, 15-25 g (8))], and neither nodules nor lymphadenopathy was detected. Furthermore, the vascularity index estimated using color Doppler (power mode) was 31.0% [reference range, <64% (9)] (Figure). A thyroid scan with ^{99m}Tc revealed a low uptake [0.29% (reference range, 0.80-1.2% (9))] in the thyroid gland, which was compatible with painless thyroiditis (Figure). No treatment was given.

Changes in the thyroid function are shown in Table. The FT4 and FT3 concentrations in January 2019 returned to the reference ranges. Her serum TSH remained undetectable. In March 2019, she became severely hypothyroid. M22-TRAb

and TBAb remained strongly positive throughout the investigation period. When she was hypothyroid, the TSAb level was decreased to just above reference range. At that time, she complained of malaise, drowsiness, amnesia, dry skin, constipation and cold intolerance, all of which were compatible with signs and symptoms typical of hypothyroidism.

Based on the clinical course and laboratory findings, a diagnosis of painless thyroiditis was finally confirmed. She was started on a daily dose of 75 μg levothyroxine, which has been continued until the present follow-up.

Discussion

We herein report a rare case of painless thyroiditis that was positive for both TBAb and TSAb during the thyrotoxic phase. To date, only one case of painless thyroiditis in which TBAb was detected in the hypothyroid phase has been reported (10).

Our case was initially thought to have GD, as she was strongly positive for M22-TRAb. However, the findings that the ^{99m}Tc uptake was suppressed and the vascularity index was normal led to a diagnosis of painless thyroiditis. Painless thyroiditis is generally considered to be a variant of Hashimoto's thyroiditis. She was also TgAb-positive suggestive of Hashimoto's thyroiditis. It is well established that two types of TSH receptor autoantibodies are associated with autoimmune thyroid disease (11). TSAbs are detected in patients with GD, whereas TBAbs are present in some patients with autoimmune primary hypothyroidism, where they are presumed to inhibit the binding of TSH to its receptor and thereby lead to thyroid hypofunction. Interestingly, Evans et al. (12) showed that a patient can simultaneously produce a mixture of blocking and stimulating TSHR autoantibodies. They demonstrated that the two antibodies had evolved separately from different B cell clones. Similarly, in the present case, TBAb and TSAb appeared at the same time, although three months later, TSAb levels had spontaneously decreased to just above the reference range in the hypothyroid phase, resulting in hypothyroidism from TBAb. Nakamura et al. (10) also reported a 24-year-old man who was positive for TBAb but negative for TSAb during the hypothyroid phase of painless thyroiditis, which differs from our case.

Recently, TBAb has been reported to be prevalent in patients with Hashimoto's thyroiditis (11%) as well as in those with GD (8%) (11). We speculate that the appearance of TBAb and TSAb in the thyrotoxic phase of painless thyroiditis may be due to the autoimmune process, as the TSAb (EIA) levels had decreased to the upper level of the reference range. In addition, high TBAb levels appeared to be associated with the pathogenesis of severe hypothyroidism, although further studies will be needed to establish the exact involvement of TBAb and TSAb in painless thyroiditis.

The author states that he has no Conflict of Interest (COI).

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