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Abstract

A case of a 40-year-old woman who was suffering from painless thyroiditis with recurrent transient thyrotoxicosis is reported. Acute exacerbations occurred four times during the past ten years, two after delivery and two after catching a cold. Serum thyroid hormones increased, though radioiodine uptake by the thyroid was very low and no inflammatory signs were observed. The histological findings of the thyroid were of atypical thyroiditis and not consistent with either chronic lymphocytic thyroiditis or subacute thyroiditis. Tanned sheep red cell hemagglutination titers for anti-thyroglobulin antibodies (TRC) and for anti-microsomal antibodies (MHA) were negative or low. The disease seems to be rare and the pathophysiology and etiology are discussed.

KEYWORDS: recurrent transient thyrotoxicosis, painless thyroiditis, hyper-thyroiditis, subacute thyroiditis, chronic lymphocytic thyroiditis

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RECURRENT TRANSIENT THYROTOXICOSIS WITH PAINLESS THYROIDITIS

— a case report —

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Abstract. A case of a 40-year-old woman who was suffering from painless thyroiditis with recurrent transient thyrotoxicosis is reported. Acute exacerbations occurred four times during the past ten years, two after delivery and two after catching a cold. Serum thyroid hormones increased, though radioiodine uptake by the thyroid was very low and no inflammatory signs were observed. The histological findings of the thyroid were of atypical thyroiditis and not consistent with either chronic lymphocytic thyroiditis or subacute thyroiditis. Tanned sheep red cell hemagglutination titers for anti-thyroglobulin antibodies (TRC) and for anti-microsomal antibodies (MHA) were negative or low. The disease seems to be rare and the pathophysiology and etiology are discussed.

Key words: recurrent transient thyrotoxicosis, painless thyroiditis, hyper-thyroiditis, subacute thyroiditis, chronic lymphocytic thyroiditis

Recently several reports of patients suffering from a peculiar thyroiditis with thyrotoxicosis have been published (1–5). The clinical and laboratory findings of these patients were painless diffuse goiter (though sometimes completely absent), transient thyrotoxicosis and low radioactive iodine uptake by the thyroid, i. e., like classical subacute thyroiditis, although the histological findings of affected thyroids are consistent with chronic lymphocytic thyroiditis. Jackson (6) proposed that such patients should be classified as having "hyperthyroiditis", while others have called the conditions painless thyroiditis or silent thyroiditis.

In Japan, there have been few reports of such patients. Now we report such a patient who had transient thyrotoxicosis four times during the past ten years, and whose thyroid was histologically consistent with neither typical chronic lymphocytic thyroiditis nor classical subacute thyroiditis.

MATERIALS AND METHODS

The levels of serum thyroxine (T4), triiodothyronine (T3) and T3 resin sponge uptake (T3RSU) were measured using commercially available kits (Dainabot Radioisotope Laboratories, Tokyo). The levels of serum thyrotropin (TSH) were measured by radioimmunoassay kit (Daiichi Radioisotope Laboratories, Tokyo). Tanned sheep red cell hemagglutination titers for anti-thyroglobulin antibodies (TRC) and for anti-microsomal antibodies (MHA) were evaluated using commercially available kits (Thyroid test and Microsome test, respectively, Fujizoki Pharmaceutical Co., Ltd., Tokyo). Five hundred micrograms of thyrotropin releasing hormone (TRH) was injected intravenously for testing TSH response to TRH. The size of the thyroid gland was expressed according to Shichijo's grading (7).

CASE REPORT

A 40-year-old woman visited our clinic because of goiter in March, 1977. Her family history and past history were not particular. She noticed weight loss (10 kg), palpitaion, finger tremor, polyphagia, hyperhidrosis and was easily fatigued and also was pointed out as having goiter by someone three months after delivery of her second child in April, 1967. She visited a certain doctor and was diagnosed as having Graves' disease (pulse rate 126/min, T3RSU 46%, PBI 14.7 μg/dl) and took antithyroid agents (Methimazole 30 mg/day 1 w, 20 mg/day 2.5 mon, then propylthiouracilum 100 mg/day 1 mon, 50 mg/day 13 mon). Three weeks after receiving the medication she became euthyroid (T3RSU 27%). When she stopped taking drugs after a year and a half, her thyroid regained normal size. In 1971, she had an abortion, but goiter did not develop.

In December, 1972, she delivered the third child and then weight loss (6 kg), palpitation and finger tremor began again. At two months post partum she became aware of her thyroid enlargement and was referred to us. On examination pulse rate was 116/min, the thyroid was firm and diffusely enlarged (grade III), but there was neither pain nor tenderness of the foreneck. Body temperature was normal. The levels of serum thyroid hormones increased and TSH was not detectable even after TRH administration and radioiodine uptake (RAIU) was very low, but erythrocyte sedimentation rate (ESR) was normal and C-reactive protein (CRP) was negative. TRC was negative and MHA titer was 1 : 1280 (Table. 1).

The cytological examination of a specimen obtained by thyroid aspiration biopsy showed many lymphocytes (Fig. 1) and histological findings of the biopsied thyroid gland showed extensive destruction of follicles with eosinophilic degeneration of epithelial cells and almost complete disappearance of follicular colloid. The infiltration of a few lymphoid cells and macrophages was observed in the follicles. Moderate interstitial fibrosis was observed with sparse lymphoid cell infiltration. These findings resembled those of subacute thyroiditis, but no giant

TABLE 1. THYROID FUNCTION TESTS AND OTHER LABORATORY FINDINGS OF THE PATIENT

	Second attack		Third attack		Fourth attack		
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	
T3RSU	42.6%	24.9%			38%	28.1%	
T4	17.3μg/dl	7.8μg/dl	13.8μg/dl	4.0μg/dl	20.0μg/dl<	4.2μg/dl	13.7μg/dl[a]
T3	385ng/dl	85ng/dl	178ng/dl	168ng/dl	355ng/dl	82ng/dl	148ng/dl[a]
TSH	u.d.[b]	7.8 μU/ml	2.4μU/ml		4.4μU/ml	57μU/ml	5.7μU/ml[a]
TRH test	no response				no response		
^{131}I uptake	0.8%	48%	0.6%	37.6%	0.55%	28%	
TRC	(−)		(−)		(−)		
Anti-Tg antibody (PEG Method)			34.5%				
MHA	×1280	(−)			(−)		×40[a]
ESR(1h/2h)	20/48	3/20	11/28		24/48		
CRP	(−)		(−)		(−)		
Cholesterol	176mg/dl				170mg/dl		
BMR	+67%						
WBC	3400						
Serum protein	7.4g/dl (-gl. 16%)						

a after thyroid hormone supplement; *b* undetectable

In each attack, thyroid hormones increased and RAIU was markedly suppressed before treatment. TRC and MHA were negative or low. ESR was within normal limits and CRP was negative.

Fig. 1, Aspiration biopsy of the thyroid (the second attack). Lymphocytes were mainly observed. (×1000)

cells and granulomatous lesions were present. On the other hand, comparing these findings with those of Hashimoto's thyroiditis, the destruction of follicles was much more marked with no regenerative follicles and the interstitial infiltration of lymphoid cells was much less (Fig. 2). She was diagnosed at that time as having chronic thyroiditis with transient hyperthyroidism and prescribed prednisolone 15 mg/day which was then gradually reduced. After three months her thyroid function became normal, though thyroid scintigram revealed slightly enlarged diffuse goiter, and six months later her goiter disappeared completely.

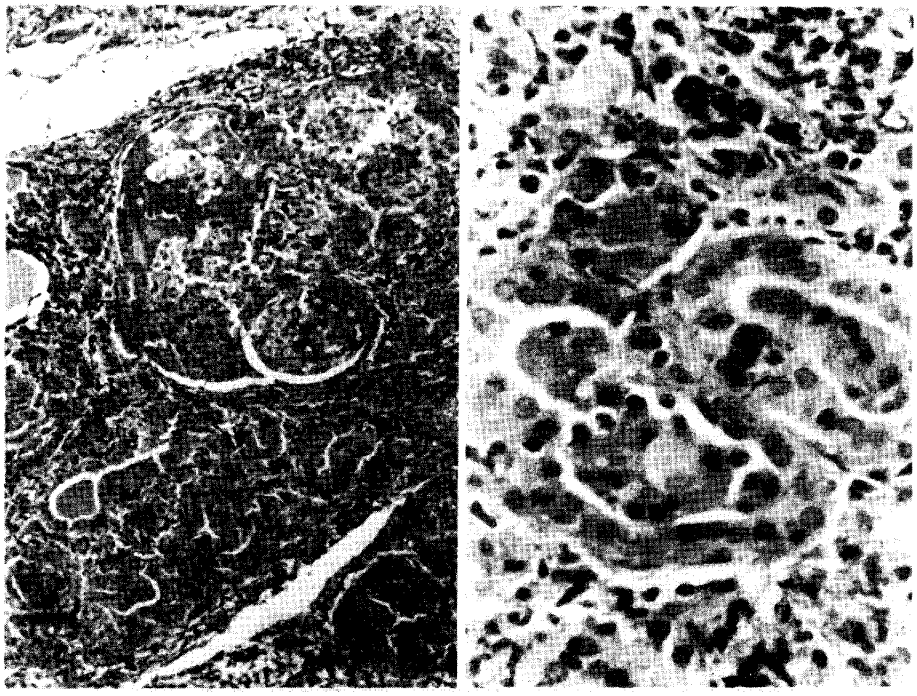

Fig. 2. Needle biopsy of the thyroid (the second attack). Extensive destruction of follicles with marked disappearance of colloid and lymphoid cell infiltration were observed. These findings are not similar to subacute thyroiditis and Hashimoto's diseasc. (left; ×100, right; ×400)

The third attack of the disease occurred in March, 1975. She caught a common cold, followed by goiter and then she consulted us. The thyroid was firm and diffusely enlarged as before. The levels of serum thyroid hormones increased slightly, but RAIU was markedly depressed again, and ESR was normal and CRP was negative. TRC was negative but anti-thyroglobulin antibody titer evaluated by ^{125}I-thyroglobulin binding capacity using polyethylene glycol method (8) was elevated to 34.5% (normal value$<$10%). Microscopic

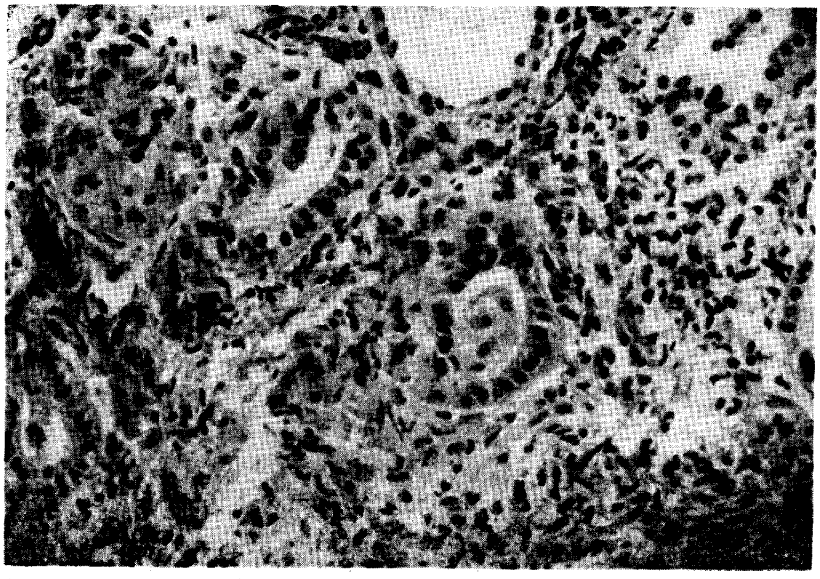

Fig. 3. Needle biopsy of the thyroid (the fourth attack). These findings are similar to those obtained at the second attack. (×200)

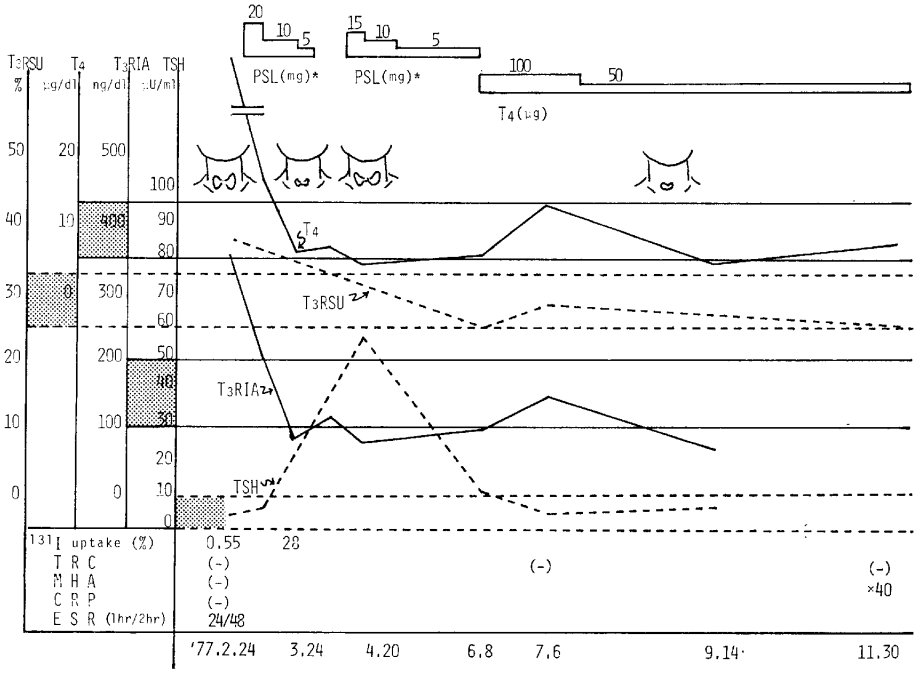

Fig. 4. Typical clinical course of her disease (the fourth attack). The shaded area indicates normal ranges of data. * PSL; prednisolone. Other abbreviations are explained in the text.

examination of an aspirated specimen from her thyroid again showed many lymphocytes. Prednisolone therapy (10 mg/day) was started again and two months later, the symptoms almost disappeared (Table. 1).

In February, 1977, she caught a common cold again and then goiter reappeared. The thyroid was firm and diffusely enlarged (grade III). Local pain or tenderness and general fever were absent. ESR was 24 mm/1 hr, CRP, TRC and MHA were all negative. T3RSU was 38%, T3 355 ng/dl, T4 above 20 μg/dl, TSH 4.4 μU/ml, and RAIU was 0.55%. There was no TSH response to TRH administration (Table 1). The histological findings of the specimen obtained by aspiration biopsy and needle biopsy were similar to those of the past attack of the disease (Fig. 3). This time prednisolone was also administered 20 mg/day. One month later the goiter became small and not palpable. The therapy was stopped because thyroid function became normal. But unexpectedly goiter began to swell again two weeks later. So prednisolone 15 mg/day was prescribed again. One week later T3, T4, TSH were 82 ng/dl, 4.2 μg/dl, 57 μU/ml, respectively and these data indicated slight hypothyroidism. Two months later she became almost euthyroid with small goiter. Since then she has been taking small amounts of thyroxine without prednisolone and remains euthyroid now (Fig. 4 and Table. 1).

DISCUSSION

It has recently been found that there are several conditions which may cause transient thyrotoxicosis. These conditions include so called "Hashitoxicosis" by Means *et al.* (9), subacute change of Hashimoto's thyroiditis and subacute thyroiditis.

"Hashitoxicosis" should be considered as an association of Graves' disease and Hashimoto's thyroiditis and consists of thyrotoxicosis with painless diffuse goiter and without any inflammatory symptoms and signs. The histological findings of the thyroid show parenchymal hyperplasia like Graves' disease and infiltration of lymphoid cells, eosinophilic degeneration of epithelial cells and interfollicular fibrosis as in Hashimoto's disease. RAIU of the patients with this disease has been demonstrated to be within normal limits or high (10–12).

In the transient subacute change with thyrotoxicosis of Hashimoto's disease, it is common that there are inflammatory symptoms such as fever, thyroid pain or tenderness, elevated ESR and positive CRP, and titers for serum thyroid autoantibodies are high. Additionally, RAIU is within normal limits or high and histological findings of the thyroid are typical chronic thyroiditis (11–14).

On the other hand, subacute thyroiditis usually manifest itself as inflammatory symptoms such as goiter with pain or tenderness, general fever and thyrotoxicosis due to leakage of thyroid hormones from damaged thyroid gland.

The clinical course of this condition is generally short, but the recurrence is not so rare and there are some reports of the patients with long clinical course (15–17). Laboratory findings of typical subacute thyroiditis are those of inflammation, increased serum thyroid hormone levels and very low RAIU due to thyroid damage. The histological findings of this disease are usually of granulomatous inflammation with multinuclear giant cells.

Moreover, there are some reports of atypical subacute thyroiditis (1, 16, 18–22). But most of these reports except Woolner's (20) did not describe the histological findings of the patients' thyroids or whether patients had thyrotoxicosis or not.

In 1975, Gluck *et al.* (2) reported cases with histologically characteristic chronic lymphocytic thyroiditis which showed temporary thyrotoxicosis with low RAIU. Since then similar cases including patients without goiter have been reported (3–5).

Jackson (6) proposed that such disease should be classified as "hyperthyroiditis"—a term that can be used to encompass subacute thyroiditis, Hashimoto's disease or other conditions, all of which may produce thyroid inflammation with transient thyrotoxicosis due to thyroid hormone leakage.

In some cases a transient hypothyroid phase may exist. There have been transient hypothyroid patients who did not undergo hyperthyroid phase (23, 24), though it is not known whether this is the same disease as mentioned above or not. It is possible that transient hypothyroidism may occur when thyroid damage is severe and regeneration of follicular cells is not enough yet. It is also possible that transient hyperthyroid phase may be overlooked by physicians in patients with transient hypothyroidism.

In considering its etiology, Dorfman *et al.* (4) concluded that one must assume that if this "syndrome" was subacute thyroiditis, 1) this was a new form both clinically and histologically, possibly due to a new virus or a variable response to a previously described virus; or 2) that patients with chronic lymphocytic thyroiditis were peculiarly prone to develop this "syndrome". They also described the possibility that this "syndrome" might be a rare and previously unrecognized form of early chronic lymphocytic thyroiditis, since the radioimmunoassayable anti-thyroglobulin antibody titers were still positive in all their patients even at late stages of recovery.

As the histological findings of our patient's thyroid gland were different from those of chronic lymphocytic thyroiditis or subacute thyroiditis and did not change to typical chronic lymphocytic thyroiditis though her clinical course extended over ten years, it is difficult to say that the disease is an early stage of chronic lymphocytic thyroiditis.

It is also interesting that this syndrome occurred at post partum (5, 24, 25).

Ginsberg and Walfish (5) reported five patients who had painless thyroiditis with transient thyrotoxicosis post partum. Thyrotoxicosis developed within 1-6 months after delivery. The thyroid of the two patients showed histologically chronic lymphocytic thyroiditis and serum anti-microsomal antibody titers were persistently elevated. These authers reported that the other three patients had painless subacute thyroiditis without thyroid biopsies and mentioned that chronic thyroiditis might occur although painless subacute thyroiditis was the underlying condition in most of their patients.

It is possible that our patient might have had this "syndrome" mentioned above subclinically before pregnancy and thyroid injury developed with transient thyrotoxicosis or hypothyroidism after delivery. However, she also had quite similar attacks after catching a cold. So the true etiology and destructive mechanism of this "syndrome" is not clear yet.

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