NOTE

Occurrence and Spontaneous Remission of Graves' Hyperthyroidism Preceded by Painless Thyroiditis

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Abstract. A 45-year-old woman was referred to our hospital because of discomfort in the cervical region. Laboratory findings revealed thyrotoxicosis with positive TSH receptor antibodies, but acute inflammatory data were absent. After three weeks the thyroid hormone levels spontaneously decreased to hypothyroid levels, and thyroidal radioactive iodine uptake (RAIU) was below normal. A needle-biopsy specimen of the thyroid gland obtained two months later showed diffuse lymphocytic thyroiditis, and she was therefore diagnosed as having had painless thyroiditis. Two months after returning to euthyroidism, a second thyrotoxicosis developed. TSH receptor antibodies remained positive, but RAIU was slightly above normal, indicating Graves' hyperthyroidism. Treatment with antithyroidal drugs was commenced but was soon discontinued due to an allergic reaction. Although only β-adrenergic antagonist was administered for treating the thyrotoxicosis, thyroid function was gradually normalized in parallel with the reduction in TSH receptor antibody. In this case, painless thyroiditis would be followed by Graves' disease and subsequent spontaneous remission.

Key words: Graves' disease, Painless thyroiditis, Spontaneous remission, Thyrotoxicosis, TSH receptor antibody

SEVERAL reports have described the development of hyperthyroidism due to Graves' disease preceded by painless thyroiditis [1-3]. Although the mechanism of this phenomenon is still unclear, the most feasible explanation is as follows: Damage to thyroid epithelial cells leads to the release of TSH receptor, thyroglobulin (Tg) and microsomal antigens, which in turn leads to the stimulation of helper T cells, inducing the production of autoantibodies to TSH receptor, antithyroglobulin (TgHA) and antimicrosomal (MCHA) antibodies [3]. In contrast, it has been reported that painless thyroiditis recurred in the same patient [3-5]. Since the therapeutic procedures for Graves' disease and painless thyroiditis are completely different, the differential diagnosis of the two disorders is very important [4].

In several reports, treatment of patients with hyperthyroid Graves' disease with only β-adrenergic antagonist drugs was followed by remission of hyperthyroidism in 16–30% of them [6]. Since β-adrenergic antagonist drugs have no antithyroid or immunosuppressive actions, these remissions are most likely spontaneous, but there is only one case report on spontaneous remission of Graves' disease preceded by painless thyroiditis [1]. We present a patient with Graves' disease occurring after painless thyroiditis whose hyperthyroidism spontaneously remitted in parallel with the change in TSH receptor antibody activity. Consideration of the clinical course of this patient...
is useful for clarifying the mechanism of the development of Graves' hyperthyroidism preceded by painless thyroiditis.

Materials and Methods

Serum levels of free thyroxine (FT₄), free triiodothyronine (FT₃), and Tg were measured by radioimmunoassay (FT₄ and FT₃, Amersham International Ltd., Amersham, Bucks, UK; Tg, Eikenkagaku, Tokyo, Japan), and TSH was measured by a two-site immunoenzymometric assay (Tosoh, Yamaguchi, Japan). TGHA and MCHA were measured with a Microtiter Particle Agglutination Test Kit (Fujirebio Inc., Tokyo, Japan). TSH binding inhibitor immunoglobulin (TBII) activity was measured by a radioreceptor assay (TRAb) with a commercially available kit (RSR Ltd., Cardiff, UK). Thyroid-stimulating antibody (TSAb) activity was determined by measuring cyclic adenosine-3',5'-monophosphate (cAMP) produced in FRTL-5 cells as an index of stimulation as previously reported [7]. Thyroid stimulating-blocking antibody (TSBAb) activity was measured by a method previously reported by Konishi and his colleagues [8], being commercially available (Otsuka Assay Lab., Tokushima, Japan). Normal values were as follows: FT₄, 0.8-2.3 ng/dl; FT₃, 2.5-6.0 pg/ml; TSH, 0.3-4.5 µU/ml; Tg, < 30 ng/ml; TGHA and MCHA, < 1 x 10²; TBII, < 15%; TSAb, < 140%; TSBAb, < 40%.

Case Report

A 45-year-old woman was referred to Fukui-ken Saiseikai Hospital in July, 1993 because of discomfort in the cervical region. There was no history of earlier thyroid diseases. She was afebrile and had no symptoms of hyperthyroidism, i.e., palpitation, excessive sweating or weight loss. On physical examination, she did not exhibit tachycardia, finger tremors, hyperhidrosis or exophthalmos. The thyroid gland was slightly enlarged with a consistency somewhat harder than normal but without tenderness. Laboratory data, including serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), were normal, with the exception of thyroid function. Serum FT₄ was normal at 2.0 ng/dl, FT₃ was slightly high at 6.8 pg/ml, and TSH was suppressed to an undetectable level (< 0.1 µU/ml), indicating a thyrotoxic state. Titer of MCHA was positive (x 25,600), but TGHA was negative. Both TBII and TSAb activities were positive (63.5% and 287%, respectively). In contrast, TSBAb activity was negative (−6.5%). After three weeks the serum FT₄ and FT₃ levels spontaneously decreased to hypothyroid levels in parallel with an increase in TSH (Fig. 1), and the serum Tg concentration decreased in parallel with the changes in FT₄ and FT₃ (Fig. 1). Late in August thyroidal radioactive iodine uptake (RAIU) was slightly below normal.
at 24 h (8.0%). Based on the above data, she was diagnosed as having had painless thyroiditis. A needle-biopsy specimen of the thyroid gland obtained in the middle of September, 1993 showed diffuse lymphocytic thyroiditis with epithelial hyperplasia in some follicles (Fig. 2), leading to a histological diagnosis of chronic lymphocytic thyroiditis.

Thereafter the serum levels of FT4 and FT3 again increased to above the normal range in parallel with the suppressed TSH level by November, 1993. She exhibited palpitation, excessive sweating, and tremor of the fingers. The size of the thyroid gland was essentially unchanged. When RAIU was reevaluated to distinguish between the occurrence of Graves' hyperthyroidism and a repeated bout of painless thyroiditis, the value obtained, 37.5%, indicated Graves' hyperthyroidism. Treatment with methimazole (MMI) (15 mg/day) and propranolol (30 mg/day) was commenced, but the administration had to be discontinued after two weeks due to an allergic reaction. Propylthiouracil (PTU; 150 mg/day) was administered to counter the reelevation of thyroid hormones after cessation of the previous drugs, but again an allergic reaction forced us to discontinue the administration of PTU after two weeks. Thereafter only propranolol (30 mg/day) was administered to treat the thyrotoxicosis. As shown in Fig. 1, the serum levels of FT4, FT3, and Tg decreased gradually in parallel with the reduction in TBII and TSAb activities. In addition, the titer of MCHA gradually decreased from × 25,600 to × 1,600. In contrast, the serum level of TSH remained suppressed at an undetectable level, and both TSAb activity and the titer of TGHA remained negative (7.7% and <100, respectively). The serum levels of both FT4 and FT3 were normalized in October, 1994, at which time TBII activity was negative.

Discussion

It is known that Graves' disease is preceded by various types of destructive thyroiditis, including subacute thyroiditis [9,10], painless thyroiditis [1-3], and radiation thyroiditis [11]. In this case, although RAIU was not measured at the time of the thyrotoxic state, the first thyrotoxicosis was likely to be due to painless thyroiditis for several reasons. Firstly, the clinical course of the first thyrotoxicosis, i.e., an initial thyrotoxic phase followed by euthyroidism and subsequent hypothyroidism, finally returning to euthyroidism, is compatible with the clinical course of painless thyroiditis. Secondly, the needle-biopsy specimen of the thyroid showed some evidence of chronic lymphocytic thyroiditis. Thirdly, the absence of acute inflammatory data suggests that the development of subacute thyroiditis is unlikely.

The evidence that TBII and TSAb activities were both positive during the period of thyrotoxicosis due to painless thyroiditis is consistent with the previous reports [1-3, 12]. Although the possibility that TBII and/or TSAb were initially positive even before the occurrence of painless thyroiditis cannot be excluded, it seems likely that production of TSH receptor antibodies was triggered by destruction of thyroid follicular cells due to painless thyroiditis. In support of this assumption, TBII activities showed an initial increase in the early phase of the first thyrotoxicosis, but the possibility that Graves' hyperthyroidism and painless thyroiditis developed simultaneously cannot be excluded completely. Recently Umena et al. [3] described a case with Graves' disease preceded by painless thyroiditis in which the changes in thyroid function and TBII were similar to those in our patient. As in our case, TBII activities in their case peaked about three months before the patient entered the second thyrotoxic state. The only difference from
our case was that an antithyroidal drug (MMI) was administered for three months after the initiation of the second thyrotoxicosis.

During the second thyrotoxicosis, RAIU was slightly high in spite of undetectable TSH levels, prompting us to make the diagnosis of Graves' disease, in which stimulation of the thyroid by TSAb is responsible for the hyperthyroidism. Hyperplasia of thyroid epithelial cells in some follicles revealed by needle biopsy performed during the hypothyroid state may reflect the effect of TSAb or TSH stimulation.

The reduction in TBII and TSAb activities may be spontaneous or due to the decrease in the release of thyroid antigens, and was considered responsible for the gradual decrease in thyroid hormones without administration of antithyroidal drugs. In several studies, treatment of patients with hyperthyroid Graves' disease with only β-adrenergic antagonist drugs was followed by remission of hyperthyroidism in 30.8% of them [6]. Since these drugs are devoid of antithyroid and immunosuppressive actions, these remissions were most likely spontaneous and part of the natural course of the disease. Noh et al. [1] described a case with spontaneous remission of Graves' hyperthyroidism preceded by hypothyroidism due to painless thyroiditis. But, unlike our case, TBII activity remained positive at the time of euthyroidism. It is not yet clear whether patients with Graves' hyperthyroidism following painless thyroiditis have a good chance of spontaneous remission or not, so that further clinical studies are required.

Changes in the balance of TSAb and TSBAb activities are known to influence the thyroid state directly [13–15], but in this case, TSBAb activity remained undetected throughout the whole clinical course.

In conclusion, since the therapeutic procedures for these two types of thyrotoxicosis are completely different, they should be carefully differentiated by RAIU and measurement of TBII and TSAb. In addition, since we believe that some patients may show spontaneous remission as in our case, caution should be exercised in treating Graves' hyperthyroidism preceded by painless thyroiditis.

References

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