

Case Report

Graves' Disease Associated with Goserelin Acetate

Shigeki MORITA, Yasuo UEDA

Internal Medicine, Japanese Red Cross-Nagasaki Atomic Bomb Hospital

We describe a case of Graves' disease associated with goserelin acetate. A 47-year-old woman experienced thyrotoxicosis during the administration of goserelin acetate, a gonadotropin-releasing hormone (GnRH)-agonist. Since the TSH receptor-antibody was positive, and a thyroid scintigram showed diffuse goiter and high uptake, she was diagnosed as having Graves' disease. 26 months after treatment with thiamazole, she recovered. We speculate that the administration of goserelin acetate may be one of the triggers of Graves' disease.

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Introduction

The syndromes of thyroid autoimmunity, including Graves' disease and painless thyroiditis, can be induced by genetic and environmental factors^{1,2)}. It has been reported that many environmental factors, for example iodine, infection, glucocorticoids, postpartum, cytokines and also sex hormones can alter the immunologic tolerance of the thyroid gland and influence thyroid autoimmunity^{3–5)}.

Gonadotropin-releasing hormone(GnRH)-agonists are recently used for the treatment of sex hormone-dependent diseases, for example mammary cancer and uterine myoma⁶⁾, as the administration of GnRH agonists can alter the secretions of gonadotropin and sex hormones. It was suggested that GnRH agonists via sex hormones may be one of the triggers of the syndromes of thyroid autoimmunity^{7,8)}.

Goserelin acetate is one of the GnRH agonists^{9,10)}. Here, we describe a case of Graves' disease associated with the administration of goserelin, and briefly re-

view the literature of GnRH agonist-induced thyroid autoimmunity.

Case report

The patient was a 47-year-old woman who had previously undergone a mastectomy for left mammary cancer (positive for estrogen and progesterone receptors) in April 1996, and had been injected with 3.6mg goserelin acetate every 4 weeks since that time. In May 1997, she exhibited general malaise, palpitations and hand tremors. She was admitted on June 19th, 1997. She had consumed no excess iodine in food, medicine or contrast media, and had taken no thyroid hormones. A physical examination on admission revealed tachycardia, hand tremors and diffuse goiter without exophthalmos. Serum concentrations of free thyroxine, free triiodothyronine and thyroid stimulating hormone were 4.0 ng/dl, 12.9 pg/ml and less than 0.05 μ IU/ml, respectively. The serum level of anti-thyroid peroxidase-antibody was positive (1:1600), and that of anti-thyroglobulin-antibody was negative. The anti-TSH receptor-antibody (TRAb) was positive (52%). A Tc-99m thyroid scintigram showed diffuse goiter and high uptake, and she was diagnosed with Graves' disease. Thiamazole was administered for 26 months and TRAb became negative (0%). After the cessation of thiamazole in September 1999, serum concentrations of thyroid hormones remained within normal levels.

Discussion

It has been reported that many environmental factors could induce the syndromes of thyroid autoimmunity, especially painless thyroiditis and Graves' disease^{1–5)}. Painless thyroiditis is induced within several months after these triggers and the duration of thyrotoxicosis is short. Although Graves' disease can also be induced by these triggers, the interval period from triggers to

Address Correspondence: Shigeki Morita, M.D.

Internal Medicine, Japanese Red Cross-Nagasaki Atomic Bomb Hospital, 3-15, Morimachi, Nagasaki, 852-8511, Japan

TEL: +81-95-847-1511 FAX: +81-95-847-8036

E-mail: morita@nagasaki-med.jrc.or.jp

the onset of thyrotoxicosis is longer than that of painless thyroiditis, and it may be induced by the difference of cellular and humoral immunity between painless thyroiditis and Graves' disease^{2,4)}.

Sex hormones are known to influence the immune system, and the fluctuation of sex hormones may be important factors in thyroid autoimmunity^{2,7,8)}. The administration of goserelin acetate induces an initial increment of serum gonadotropin, in association with a corresponding increment in the serum levels of estrogen and progesterone^{9,10)}. The prolonged administration of goserelin suppresses gonadotropin secretion by down regulation of GnRH receptors and inhibits estrogen and progesterone secretion. Thus, the fluctuation of serum levels of gonadotropin and sex hormones induced by GnRH agonists may trigger the development of the syndromes of thyroid autoimmunity.

In this case, a thyroid scintigram during thyrotoxicosis revealed a high uptake of diffuse goiter. Moreover, there was positive TRAb, and she was diagnosed with Graves' disease. Since the onset of Graves' disease occurred during the administration of goserelin and without other environmental factors, we speculated that Graves' disease might be associated with goserelin. Previous reports have shown two patients with the syndromes of thyroid autoimmunity induced by GnRH agonists. One was our patient in whom thyrotoxicosis occurred 2 months after the administration of buserelin, and the other case occurred 4 months after leuprorelin acetate administration^{7,8)}. Both cases developed GnRH agonist-induced painless thyroiditis within several months. On the other hand, in this case, there was a longer period from starting goserelin to the onset of clinical thyrotoxicosis of Graves' disease. It is suggested that the appearance of thyrotoxicosis by GnRH agonist-induced Graves' dis-

ease may take longer than by painless thyroiditis, as with other environmental factors-induced syndromes of thyroid autoimmunity¹⁻⁴⁾. On the other hand, this patient is the first reported case of Graves' disease and third case of the syndromes of thyroid autoimmunity induced by GnRH agonists. Therefore, it may be needed more patients for the further examination of the relationship between GnRH agonists and the syndromes of thyroid autoimmunity.

In summary, the administration of GnRH agonists is thought to be one of the triggers of Graves' disease. Since there are many patients with subclinical thyroid autoimmunity, GnRH agonist-therapy should be considered carefully in these patients.

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