NOTE

Transient Thyrotoxicosis and Hypothyroidism Following Administration of the GnRH Agonist Leuprolide Acetate

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Abstract. A 45-year-old woman with chronic idiopathic thrombocytopenic purpura was given monthly injections of the GnRH agonist leuprolide acetate for the treatment of uterine leiomyoma. Two weeks after the fifth injection, she showed mild symptoms of thyrotoxicosis. At that time, serum thyroxin (T4) and triiodothyronine (T3) levels were elevated whereas TSH level was suppressed. Anti-thyroglobulin (anti-Tg) and anti-thyroid peroxidase (anti-TPO) antibodies were positive, whereas TSH binding inhibitory immunoglobulin (TBII) was undetectable. Two months later, serum T4 and T3 levels spontaneously decreased below the normal ranges. Five months after the onset of the disease, they returned to normal without any treatment. Anti-TPO and anti-Tg antibodies gradually decreased during the clinical course. Thus, the present case was indicated to be an instance wherein silent thyroiditis developed after leuprolide acetate administration. This is the first report to demonstrate the association of thyroid disorder with leuprolide injection.

Key words: GnRH, Leuprolide acetate, Silent thyroiditis

(*Endocrine Journal* 47: 783–785, 2000)

GnRH agonist is now used for the treatment of a wide variety of sex hormone-related diseases such as uterine leiomyoma, endometriosis, prostatic cancer, and precocious puberty [1]. Administration of the GnRH agonist leuprolide acetate is associated with an initial increase in serum LH and FSH levels, associated with corresponding rise in serum estrogen and progesterone concentrations [2]. Prolonged administration of this drug inhibits gonadotropin secretion from the pituitary gland by causing desensitization by down-regulation of GnRH receptors, and thus decreases sex hormone secretion from the gonads.

In the present case report, we describe a woman who developed transient thyrotoxicosis followed by

transient hypothyroidism after she was given GnRH agonist leuprolide acetate for the treatment of uterine leiomyoma.

Case Report

A 45-year-old Japanese woman complained of hypermenorrhea with regular menstrual cycles, when uterine leiomyoma was diagnosed. At 42 years old, she had been diagnosed as chronic idiopathic thrombocytopenic purpura (ITP). Her platelet count was $42\text{--}93 \times 10^9/\text{l}$ with increased level of platelet-associated IgG (303 ng/ 10^7 platelets). She had no medical treatment for these 3 years. For the treatment of uterine leiomyoma, subcutaneous injection of leuprolide acetate (3.75 mg/month) was started. After the second injection, her menses ceased. Two weeks after the fifth injection, she showed symptoms such as increased sweating, fatigue, increased appetite, and weight loss (–1 kg during one month). Blood pressure was 132/78 mmHg and pulse was 92/min.

Received: June 2, 2000

Accepted: August 7, 2000

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She had neither thyroid enlargement nor neck pain. Laboratory tests revealed no signs of inflammation. Hepatic and renal function was normal. White blood cell count and red blood cell count were normal, whereas platelet count was slightly decreased ($88 \times 10^9/l$). Serum free thyroxine (T4) (32 pmol/l, normal 11–23 pmol/l) and triiodothyronine (T3) (12 pmol/l, normal 3.7–6.6 pmol/l) were elevated. Thyroid-stimulating hormone (TSH) ($<0.01 \mu\text{U/ml}$, normal $0.6\text{--}4.9 \mu\text{U/ml}$) was suppressed. TSH binding inhibitory immunoglobulin (TBII) (7%, normal $<12\%$) was negative, whereas anti-thyroglobulin (anti-Tg) antibody (31 U/ml, normal $<0.3 \text{ U/ml}$) and anti-thyroid peroxidase (anti-TPO) antibody (120 U/ml, normal $<0.3 \text{ U/ml}$) were positive.

The clinical symptoms spontaneously disappeared two weeks after the onset of the present illness. At that time, 24h-thyroid radioiodine (^{131}I) uptake was within normal range (23.8%), indicating recovery from thyroiditis. Two months later, her thyroid function was decreased below the normal (free T4, 6.4 pmol/l; free T3, 2.9 pmol/l; TSH, $83.6 \mu\text{U/ml}$) (Fig. 1), when her thyroid gland was slightly enlarged. Five months later, her thyroid function returned to normal without any treatment, associated with the reduction of the thyroid size. Anti-TPO antibody and anti-Tg antibody levels were gradually decreased during the clinical courses (Fig. 1).

Discussion

Sex steroids are known to influence the immune system, which may be a part of the mechanisms underlying the sexual dimorphism in autoimmune diseases including autoimmune thyroid diseases [3, 4]. However, there has been no direct evidence that the sex hormones are involved in the development of the autoimmune thyroid diseases.

The present case developed transient thyrotoxicosis followed by transient hypothyroidism after the administration of the GnRH agonist leuprolide acetate. Serum TBII level was not elevated in her thyrotoxic state, suggesting that the transient thyrotoxicosis in this patient is not caused by Graves' disease. The clinical course of the thyroid status in this patient appears to resemble that observed after delivery in patients with autoimmune thyroid diseases [5]. The postpartum thyroiditis is now considered to be iden-

Fig. 1. Changes in serum levels of TSH, free thyroxine (T4), anti-thyroid peroxidase (TPO) antibody (Ab), and anti-thyroglobulin (Tg) Ab with time from the first injection of leuprolide acetate. Control ranges of TSH and free T4 are shown as shaded area.

tical to silent thyroiditis developed in the postpartum period. Thus, we speculated that our case presented silent thyroiditis after the leuprolide administration was introduced. Our patient had been diagnosed as chronic ITP three years ago. Since autoimmune thyroid disease is sometimes associated with ITP [6], the present case may have already had euthyroid autoimmune thyroiditis as a background disorder.

Administration of leuprolide acetate is associated with an initial increase in serum LH and FSH levels, in association with corresponding rise in serum estrogen and progesterone levels [2]. However, prolonged administration of leuprolide acetate inhibits pituitary gonadotropin secretion by down-regulation of GnRH receptors, resulting in suppression of estrogen and progesterone secretion from the ovary [2]. Thus, the leuprolide acetate-induced alteration in serum levels of the gonadotropins and the sex steroids is indicated to trigger the development of silent thyroiditis in this patient. In the present case,

the clinical symptoms became evident two weeks after the fifth injection of this drug. Therefore, hypo-estrogenic state rather than initial gonadotropin surge is suggested to be involved in the pathogenesis of the silent thyroiditis developed in this patient. This is in contrast with a recent report of a patient demonstrating exacerbation of lupus nephritis immediately after the first injection of leuprolide, indicating that estrogen surge precipitated an acute flare of lupus nephritis [7]. In this relation, adverse effects associated with the initial gonadotropin surge have been reported, such as flares of endometriosis [8] and pituitary apoplexy [9]. Since in mice GnRH

has been shown to possess immunostimulatory properties independently of gonadal steroids [10, 11], it is also possible that the direct effect of the GnRH agonist on immune response may have induced the thyroiditis in our patient.

To date, there is no report showing the association of thyroid dysfunction with leuprolide injection. The present case revealed a possible association of abrupt change in levels of gonadotropins and sex hormones with the development of silent thyroiditis. The physicians need to pay careful attention to thyroid status when GnRH agonists are given to patients having autoimmune thyroid disease.

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