Transient thyrotoxicosis following prolonged use of gonadotropin-releasing hormone agonist in women with endometriosis – a case report

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Abstract

This paper reports two cases showing transient thyrotoxicosis caused by prolonged use of gonadotropin-releasing hormone (GnRH) agonist. Case 1, a 31-year-old woman, was administered GnRH-agonist (leuprorelin acetate) for treatment of endometriosis. After four months she showed thyroid dysfunction. Case 2, a 43-year-old woman, who was previously diagnosed with chronic thyroiditis, was treated with GnRH-agonist (nafarelin acetate) for her endometriosis. Five months later, her thyroid functions worsened. After discontinuation of the GnRH-agonist, thyroid function of both cases recovered. In selected patients, who are on GnRH-agonist, attention to thyroid function is important.

Key words: GnRH-agonist, endometriosis, thyroid grand, thyroiditis.

Introduction

Administration of gonadotropin-releasing hormone (GnRH) agonists (i.e. leuprorelin acetate, buserelin acetate and nafarelin acetate) is a common treatment for endometriosis and uterine fibromas. In recent years, some cases that appeared as thyroid dysfunction following administration of GnRH-agonist have been reported [1-6]. All these cases were treated by GnRH-agonist for various causes such as dysmenorrhoea, abnormal genital bleeding and endometriosis. With prolonged administration of GnRH-agonist, the GnRH receptors on the pituitary gland were desensitized with subsequent very low levels of oestrogen and progesterone, as if in a post-menopausal state. It was suggested that this low oestrogen level might be a trigger of thyroiditis. Recently, we had two cases of unexpected thyrotoxicosis, that occurred during the long-term administration of GnRH-agonist in the treatment of severe dysmenorrhoea. In this case report, we describe these two cases in detail, and caution clinicians to be circumspect in their use of GnRH-agonist.

Case reports

Case I

A 31-year-old infertile woman with a regular menstrual cycle presented with severe intractable dysmenorrhoea. Her basal gonadotropin levels, prolactin level and thyroid function were normal. She gave no family history of thyroid disease. She had been diagnosed with endometriosis at 27 years of age, with bilateral ovarian endometriomas, but had not undergone any medical treatment. She finally decided to seek medical treatment for her endometriosis. Treatment with GnRH-agonist (leuprorelin acetate, Leuplin® 1.88 mg every 4 weeks, Takeda, Osaka) was commenced. After the 3rd injection of leuprorelin acetate, a slight thyroid swelling appeared and the value of anti-thyroperoxidase (TPO) and anti-thyroglobulin (TG) antibodies was slightly elevated (anti-TPO 2.6 U/ml, normal range <0.3 U/ml, anti-TG 5.5 U/ml, normal range <0.3 U/ml), but the values for serum FT4 (1.6 ng/dl, normal range 0.7-1.5 ng/dl), FT3 (2.3 pg/ml, normal range 1.7-3.7 pg/ml) and TSH (0.76 μIU/ml, normal rage 0.35-4.94 μIU/ml) were almost normal.

A laparoscopic endometrial cystectomy was performed, and additional administration of leuprorelin acetate was done for her severe endometriosis (stage IV of revised AFS classification) [7]. Four weeks after the additional administration of GnRH-agonist, severe symptoms such as mild tachycardia, diaphoresis and loss of body weight appeared. Clinically, her thyroid was remarkably swollen, and serum FT4 (2.2 ng/dl) and FT3 (6.4 pg/ml) levels had increased, accompanied by a very low TSH value (0.014 μIU/ml). Based on these results, she was diagnosed as having thyrotoxicosis, and leuprorelin acetate was discontinued. The clinical symptoms gradually improved without further medical treatment. Six months later her thyroid function recovered to a normal range (Table I).

Case II

A 43-year-old woman, gravida 2, para 2, with regular menstrual cycles, complained of severe dysmenorrhoea due to endometriosis. She had also been diagnosed with chronic thyroiditis (Hashimoto's thyroiditis), but her thyroid functions were normal without medication. She gave no family history of thyroid disease. Although she had a unilateral large endometrial cyst, she did not agree to laparoscopic surgery. She then decided to have GnRH-agonist (300 μg per day of nafarelin acetate, Nasanyl®, Astellas, Tokyo) therapy. Five months after the administration of nafarelin acetate, her thyroid gland was slightly enlarged. Her FT4 (2.3 ng/ml) and FT3 (6.8 pg/ml) levels were elevated with a significantly low value of TSH (0.01 μIU/ml) and TSH binding inhibitor immunoglobulin (TBII, normal range <10%) –4.8%. The anti-microsomal antibody was very high (6400, normal range <100). Based on these results, she was diagnosed as having painless thyroiditis. Administration of nafarelin acetate was stopped immediately, and potassium iodide was administered for the treatment of the painless thyroiditis. One month later, her thyroid function recovered to a normal range (Table II).

Discussion

In recent years, there have been several reports describing thyroid dysfunction, triggered by the administration of GnRH-agonist [1-6]. Sonoda et al. reported painless thyroiditis that appeared after the administration of leuprolide acetate [1]. This patient showed normal TSH, FT3 and FT4 levels but positive anti-TG antibodies. She was diagnosed with Hashimoto's thyroiditis. The clinical symptoms (palpitations, general fatigue and disconcertment) improved without medical treatment. In another case reported by Fukuda et al., painless thyroiditis also appeared after the administration of nafarelin acetate

Table I. Changes in serum levels of FT4, FT3 and TSH of case 1

	Two months after GnRHa*7 initiation	Four months after GnRHa initiation	Five months after GnRHa initiation	Nine months after GnRHa initiation
FT4* [ng/dl]	1.64	2.20	1.65	1.15
FT3*2 [pg/ml]	2.3	6.4	4.7	2.9
TSH*3 [μIU/ml]	0.76	0.014	<0.001	2.1
TRAb*4	NT*8	NT*8	negative	NT*8
TPOAb*5	2.6	NT*8	<0.3	NT*8
TGAb*6	5.5	NT*8	NT*8	34.2

** – free thyroxine, *2 – free triiodothyronine, *3 – thyroid-stimulating hormone, *4 – thyrotropin receptor antibodies, *5 – anti-thyroperoxidase antibody, *6 – anti-thyroglobulin antibody, *7 – gonadotropin-releasing hormone, *8 – not tested*

The serum levels of FT4, FT3 and TSH were measured using chemiluminesent immunoassay (DPC immrise HS-free T4, HS-free T3, HS-TSH, Diagnostic Products Corporation EURO/DPC Ltd.). TRAb was measured by radioreceptor assay kit (CosmicIII, RSR limited, UK). TPOAb and TGAb were measured by radioreceptor assay kit [CosmicII (500), CosmicII RSR limited, UK]

Table II. Changes in serum levels of FT4, FT3 and TSH of case 2

	Five months after GnRHa*5 initiation	One month after administration of iodide	Two months after administration of iodide
FT4* (ng/dl)	2.3	1.0	0.70
FT3*2 (pg/ml)	6.8	2.5	1.37
TSH*3 (μIU/ml)	0.01	0.018	3.68
TBII*4 (%)	–4.8	NT*6	NT*6
Anti-microsomal antibody (times)	6400	NT*6	NT*6

** – free thyroxine, *2 – free triiodothyronine, *3 – thyroid-stimulating hormone, *4 – TSH-binding inhibitory immunoglobulin, *5 – gonadotropin-releasing hormone, *6 – not tested*
TBII was measured by radioreceptor assay kit (CosmicIII, RSR limited, UK). Anti-microsomal antibody was measured by particle agglutination kit (SERODIA®-AMC, FUJIREBIO, Japan)

Table III. Reported cases of transient thyroiditis induced by administration of GnRH agonist

References (years)	Age [years]	Induction for GnRH agonist treatment	Drug	Administration period until onset [months]	Complication of autoimmune disease
Fukuda (1999)	20	endometriosis	nafarelin acetate	6	basedow
Sonoda (1999)	34	endometriosis	leuprorelin acetate	4	chronic thyroiditis
Kasayama (2000)	45	uterine fibroma	leuprorelin acetate	5	ITP*
Tanaka (2000)	37	adenomyosis	buserelin acetate leuprorelin acetate	6	none
Amino (2003)	49	uterine fibroma	buserelin acetate	4	basedow
	41	uterine fibroma	leuprorelin acetate	4	basedow
	29	endometriosis	buserelin acetate	4	ITP*
Eyal (2004)	9	precocious puberty	leuprorelin acetate	8	none

** – idiopathic thrombocytopenic purpura*

[2], but no abnormality of thyroid function was observed. On the other hand, Eyal et al. reported that leuprolide acetate induced hypothyroidism in a patient with precocious puberty and cautioned care with use of GnRH-agonist for patients who have autoimmune thyroid disease [5, 8].

Painless thyroiditis was defined as inflammation of the thyroid gland characterized by passing hyperthyroidism, followed by hypothyroidism and recovery. Our assumption is that this prolonged low oestrogen state might be a trigger for exacerbation of autoimmune thyroiditis, similar to what is sometimes seen as transient postpartum or postmenopausal thyroiditis.

To our knowledge, so far 8 cases of transient thyrotoxicosis following administration of GnRH-agonist have been reported (Table III) [1-6]. Surprisingly, 7 of these 8 patients were Japanese women. The reason for this ethnic preponderance is uncertain; however, it possibly points to a higher prevalence of autoimmune thyroid disease (Hashimoto's thyroiditis) in Japanese women.

GnRH-agonist, an effective agent in the treatment of endometriosis, includes various side effects. For safe use, GnRH-agonist was used in tandem with other drugs, such as parathyroid hormone [9], and the cancer risks of these fertility drugs were studied [10]. A possibility of an induced transient hyperthyroid

state followed by a hypothyroid state should be carefully looked for in patients on GnRH-agonist with associated hypo-oestrogenic state, caused by its prolonged use.

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