INTERNAL MEDICINE

□ CASE REPORT □

Suppression of the Hypothalamic-pituitary-adrenal Axis by Maximum Androgen Blockade in a Patient with Prostate Cancer

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Abstract

A 78-year-old Japanese man showed suppression of the hypothalamic-pituitary-adrenal axis during maximum androgen blockade (MAB) therapy including chlormadinone acetate (CMA) for prostate cancer. After stopping the MAB therapy, both the basal ACTH level and the response to CRH recovered. While no reports have indicated that CMA suppresses the hypothalamic-pituitary-adrenal axis in patients with prostate cancer, CMA has been shown to inhibit this axis in animals. These observations suggest that we must monitor the hypothalamic-pituitary-adrenal axis in patients treated with CMA, especially under stressful conditions.

Key words: hypothalamic-pituitary-adrenal axis, adrenal insufficiency, chlormadinone acetate, prostate cancer

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Introduction

The suppression of the hypothalamic-pituitary-adrenal axis is a common clinical problem typically attributed to the exogenous administration of drugs with glucocorticoid activity (1). Despite the suppression of endogenous cortisol production and secretion, these agents usually do not cause clinical problems associated with adrenal insufficiency due to the glucocorticoid activity of the administered drugs. However, patients who have been treated with these drugs for a long time are likely to experience adrenal insufficiency due to stress of some sort if the administrated dose is low or after the cessation of the drugs.

Maximum androgen blockade (MAB) therapy is the mainstay treatment for advanced prostate cancer (2, 3). In clinical practice, several therapeutic strategies for MAB are used, such as surgical castration, or the administration of gonadotropin-releasing hormone (GnRH) agonists or synthetic progestogens such as anti-androgens (4). Some synthetic progestogens have structural similarities to cortisol (5, 6), and several reports have cited the adrenal dysfunction or suppression of the hypothalamic-pituitary-adrenal axis induced by synthetic progestogens in both animals and humans (7, 8).

In this report, we describe a unique case in which a prostate cancer patient developed reversible suppression of the hypothalamic-pituitary-adrenal axis during MAB therapy including chlormadinone acetate (CMA).

Case Report

A 78-year-old Japanese man was admitted to our hospital due to difficulties in controlling his diabetes mellitus. He was diagnosed with type 2 diabetes mellitus at the age of 60 and had been on nutritional therapy and anti-diabetic medication. Almost simultaneously, he started antihypertensive drugs and statins. He was also found to have prostate cancer

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Table 1. The General Laboratory Findings.

		(reference range)			(reference range)
Urinalysis			*Blood biochemistry*		
pH	5.5		Total protein (g/dL)	6.7	(6.5-8.2)
Specific gravity	1.017		Albumin (g/dL)	3.8	(3.9-4.9)
Sugar	(-)		Aspartate aminotransferase (U/L)	16	(10-35)
Protein	(+/-)		Alanie aminotransferase (U/L)	14	(5-40)
Urobilinogen	(+/-)		Alkaline phosphatase (U/L)	214	(100-340)
Ketone body	(-)		Lactate dehydrogenase (U/L)	232	(110-220)
Occult blood	(+/-)		Total bilirubin (mg/dL)	1.2	(0.0-1.0)
			γ-glutamyl transpeptidase (U/L)	28	(0-60)
Complete blood count			Creatine kinase (U/L)	113	(40-200)
White blood cells(/μL)	7,100	(4,000-9,000)	Blood urea nitrogen (mg/dL)	20	(8-20)
Neutrophils(%)	50.1		Creatinine (mg/dL)	1.13	(0.5-1.1)
Basophils(%)	0.4		Uric acid (mg/dL)	4.4	(3.0-7.0)
Eosinophils(%)	4.5		Sodium (mEq/L)	140	(135-146)
Lymphocytes(%)	37.9		Potassium (mEq/L)	4.0	(3.5-4.8)
Monocytes(%)	5.6		Chloride (mEq/L)	105	(98-108)
Red blood cells(/μL)	451×10^4	($450\text{-}550\times10^4$)	C-reactive protein (mg/dL)	<0.05	(<0.3)
Hemoglobin(g/dL)	14.0	(14.0-17.0)	Triglyceride (mg/dL)	92	(35-150)
Hematocrit(%)	42.3	(41-51)	LDL-cholesterol (mg/dL)	77	(70-140)
Platelets(/μL)	22.2×10^4	($15\text{-}35\times10^4$)	HDL-cholesterol (mg/dL)	47	(40-100)
			Serum glucose (mg/dL)	112	(60-110)
			Glycosylated hemoglobin (%)	8.6	(4.6-6.2)
			Prostate specific antigen (ng/mL)	1.05	(<4.00)

The normal basal ranges are indicated in parentheses.

Table 2. The Endocrinological Data-1.

			(reference range)
ACTH	5.1	pg/mL	(7.7-63.1)
Cortisol	0.8	μg/dL	(6.4-21.0)
DHEA-S	<2	μg/dL	(5-253)
UFC	5	μg/day	(11.2-80.3)
PRA	3.1	ng/mL/hr	(<2.7)
Aldosterone	139	pg/mL	(29.9-159)
GH	<0.05	ng/mL	(<0.17)
IGF-1	176	ng/mL	(46-172)
PRL	5.7	ng/mL	(1.5-9.7)
TSH	3.23	μU/mL	(0.65-5.55)
Free T_3	3.3	pg/mL	(2.30-3.70)
Free T_4	1.45	ng/dL	(0.93-1.75)
LH	<0.1	mIU/mL	(1.1-8.8)
FSH	4.4	mIU/mL	(0.9-12.0)
Free testosterone	<0.6	pg/mL	(4.5-16.7)

The normal basal ranges are indicated in parentheses.

GRH/TRH/CRH test

Minutes	0	30	60	90	120
GH (ng/mL)	0.39	10.64	9.29	4.25	2.23
PRL (ng/mL)	5.7	31.4	33.4	25.5	12.4
TSH (μU/mL)	1.24	11.0	20.93	17.96	11.43
ACTH (pg/mL)	5.1	15.1	15.1	15.5	14.0
Cortisol (μg/dL)	1.2	1.0	1.3	1.7	1.4

GRH 100μg, TRH 500μg, CRH 100μg, intravenous bolus.

ACTH: adrenocorticotropic hormone, DHEA-S: dehydroepiandrosterone sulfate, UFC: urinary free cortisol, PRA: plasma renin activity, GH: growth hormone, IGF-1: insulin-like growth factor-1, PRL: prolactin, TSH: thyroid-stimulating hormone, Free T_3: free triiodothyronine, Free T_4: free thyroxine, LH: luteinizing hormone, FSH: follicle-stimulating hormone, GRH: growth hormone-releasing hormone, TRH: thyrotropin-releasing hormone, CRH: corticotropin-releasing hormone.

at 70 years of age, and his clinical stage was T3N0M0. He started MAB therapy using CMA at 100 mg per day and leuprorelin acetate at 11.25 mg every 3 months from March 2004.

The patient's glycosylated hemoglobin (HbA1c) level rose to 8.6% when he was admitted in January 2010. His height and body weight were 164 cm and 69.5 kg, respectively (body mass index: 25.8 kg/m^2). His waist circumference was 110 cm, but no physical signs of Cushing's syndrome were observed. His blood pressure was around 120/70 mmHg with 80 mg valsartan and 10 mg amlodipine per day. Only mild polyneuropathy was observed as a diabetic complication. The results of the general laboratory examinations are summarized in Table 1. There were no specific abnormalities except for the elevation of serum creatinine and HbA1c. He received insulin and nutritional therapy during the hospitalization. He lost about 3 kg of his body weight and achieved a good glycemic control by the time of discharge.

We also conducted endocrinological examinations in order to rule out a hormonal cause for his diabetes mellitus (Table 2). Low basal ACTH (5.1 pg/mL) and cortisol (0.8 μg/dL) levels were detected. A further analysis indicated that the serum dehydroepiandrosterone sulfate (DHEA-S) and urinary free cortisol (UFC) levels were also low. These findings led us to consider the possibility of the suppression of the hypothalamic-pituitary-adrenal axis, although no symptoms or signs of adrenal insufficiency were evident. The levels of free testosterone were low, as expected with MAB therapy. The slightly elevated level of insulin-like growth factor-1 (IGF-1) was not due to acromegaly, as the serum growth hormone (GH) was suppressed to <0.4 ng/mL on the oral glucose tolerance test (data not shown). Magnetic resonance imaging (MRI) of the hypothalamus and pituitary gland showed no abnormalities. The indirect immunofluores-

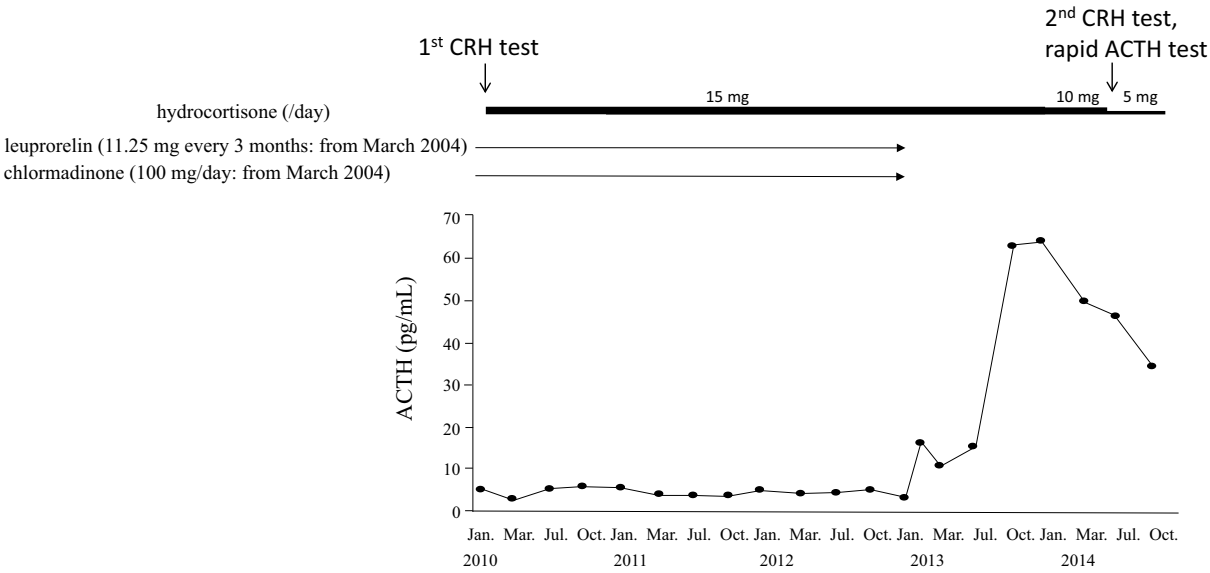

Figure. **The changes in the serum ACTH level and doses and durations of the drugs administered from 2010 to 2014.**

Table 3. **The Endocrinological Data-2.**

CRH test					
Minutes	0	30	60	90	120
ACTH (pg/mL)	74.6	161.4	160.0	109.3	91.3
Cortisol (μg/dL)	7.7	10.2	9.3	9.2	8.7

CRH 100 μg, intravenous bolus.

Rapid ACTH test			
Minutes	0	30	60
Cortisol (μg/dL)	9.1	13.3	14.8

tetracosactide 250 μg, intravenous bolus.

cent antibody technique using rat pituitary cell antigen (SRL, Tokyo, Japan) showed no anti-pituitary antibody 1. The ACTH and cortisol levels were not markedly increased by the intravenous injection of corticotropin-releasing hormone (CRH). GH, prolactin (PRL), and thyroid-stimulating hormone (TSH) adequately responded to GH-releasing hormone (GRH) and thyrotropin-releasing hormone (TRH) (Table 2). Given these findings, we started the patient on a daily dose of 15 mg hydrocortisone to prevent the manifestation of adrenal insufficiency, since there had been no reports of glucocorticoid-like effects of CMA in humans.

MAB therapy was discontinued in January 2013 at the age of 81 because the patient showed a good clinical course with no evidence of recurrence of prostate cancer. After the cessation of MAB therapy, the basal levels of ACTH gradually increased (Figure). To reassess the condition of the hypothalamic-pituitary-adrenal axis, he was again admitted to our hospital in May 2014 at the age of 83. The basal ACTH level was high and responded well to CRH; however, the responses of serum cortisol to CRH and tetracosactide were still insufficient (Table 3). However, the peak cortisol level in response to CRH was clearly higher than that observed in the first CRH test. No symptoms of adrenal insufficiency were observed during the tapering of hydrocortisone. These findings indicated that the patient had been suffering from the suppression of the hypothalamic-pituitary-adrenal axis during his long-term MAB therapy.

Discussion

MAB therapy is the standard treatment for managing advanced prostate cancer (2, 3). In clinical practice, several therapeutic strategies for MAB are used, such as GnRH agonists and oral anti-androgens. Cryptoterone acetate (CPA) and CMA are synthetic progestogens used in MAB therapy and have structural similarities to cortisol. These compounds are known to be capable of impairing the adrenal function through the negative feedback inhibition of the hypothalamic-pituitary-adrenal axis in animal models (5-7). In addition, synthetic progestogens have been shown to act via glucocorticoid receptors as both agonists and antagonists in *in vitro* models (9, 10). Several reports have also been published regarding the suppression of the hypothalamic-pituitary-adrenal axis and/or gludcocorticoid-like activity induced by synthetic progestogens in humans (8, 11-13). These reports stated that the suppression of the hypothalamic-pituitary-adrenal axis by synthetic progestogens is dose-dependent, and most patients have no symptoms during MAB therapy because these compounds exert a range of glucocorticoid activities. However, some reports have shown that steroidal anti-androgens may cause adrenal insufficiency, especially after the cessation of long-term use of these compounds (8, 13).

CMA, also known as steroidal anti-androgen therapy, has been reported to be a cause of the suppression of the hypothalamic-pituitary-adrenal axis in animal models (5, 14). However, CMA did not influence the adrenal cortical function in patients with benign prostatic hypertrophy or carcinoma for up to 6 months (15). Only one report

has been published concerning the suppression of the hypothalamic-pituitary-adrenal axis or the impairment of the adrenal function in patients treated with CMA. Two cases of congenital adrenal hyperplasia were reported to have decreased ACTH levels by CMA (16). The current case may have suffered from the suppression of the hypothalamic-pituitary-adrenal axis due to a relatively long-term treatment with a regular dose of CMA for prostate cancer.

The suppression of the hypothalamic-pituitary-adrenal axis induced by inhaled corticosteroids with low systemic glucocorticoid activity has been reported to correlate with both treatment duration and dosage (17). However, whether or not the glucocorticoid-like activity of CMA differs among individuals is unknown. The present patient did not show symptoms or signs of adrenal insufficiency due to the glucocorticoid-like activity of CMA during MAB therapy. However, the basal cortisol levels and the response of cortisol to CRH or ACTH were still low at 18 months after stopping MAB therapy. The administration of hydrocortisone may have prevented the development of adrenal insufficiency in the present case after the cessation of MAB.

In summary, we reported the first case of a patient suffering from the suppression of the hypothalamic-pituitary-adrenal axis likely induced by CMA for prostate cancer. This case highlights the need to monitor the function of the hypothalamic-pituitary-adrenal axis in patients treated with CMA, especially under stressful conditions after the cessation of CMA.

The authors state that they have no Conflict of Interest (COI).

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