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CASE REPORT AND REVIEW

Addison's disease with pituitary hyperplasia: a case report and review of the literature

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Abstract This case study describes a 33-year-old man with Addison's disease who presented with increased plasma adrenocorticotropic hormone (ACTH), normal plasma cortisol, and absent diurnal rhythms. Magnetic resonance imaging (MRI) indicated pituitary hyperplasia. Conventional hydrocortisone replacement therapy may not inhibit high ACTH levels in the morning; however, replacing hydrocortisone with dexamethasone achieved good therapeutic results.

Keywords Addison's disease · Hyperplasia · Pituitary · Replacement therapy

Introduction

Chronic hypoadrenocorticism (Addison's disease) mainly presents as fatigue, muscle weakness, weight loss, vomiting, skin pigmentation, increase in plasma adrenocorticotropic hormone (ACTH), and decrease in plasma cortisol. However, few patients present with normal plasma cortisol and absent diurnal rhythms. Pituitary ACTH cell hyperplasia or adenomas [1, 2] may occur in patients who suffer from Addison's disease but have not been treated for a long time or who have received conventional hormone replacement therapy. In this study, we describe a patient with Addison's disease who presented with increased plasma ACTH, normal plasma cortisol, and absent diurnal rhythms, accompanied by pituitary hyperplasia. Hormone levels and changes in pituitary imaging after treatment are reported.

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Case report

A 33-year-old male patient was admitted to our hospital due to progressive skin pigmentation over 10 years and 3-year weight loss and marasmus. More than 10 years previously, the patient had developed facial skin pigmentation without any obvious cause, then his skin color deepened, extending gradually to the fore limbs and trunk without itching, rash, night sweats, nausea, or vomiting. Therefore, he did not go to the hospital for treatment. Three years previous, he began to develop weight loss, soreness in the waist area and marasmus with over 5 kg weight loss, poor appetite, no appetite for salty food, no nausea or vomiting, and more obvious deepening in skin color; still he did not go in for treatment. One year previous, his skin pigmentation had become aggravated and was accompanied by minor abdominal pain; gastroscopy in a local hospital showed "superficial gastritis." More than 10 days previous, he had come to the dermatology department of our hospital and it was found that his plasma ACTH (both 8 a.m. and 4 p.m.) was >1,250 pg/ml (reference range: 0–46 pg/ml), his cortisol at 8 a.m. was 8.7 μg/dl and at 4 p.m. was 7.16 μg/dl (reference range: 5–25 μg/dl), so he was hospitalized. The patient was once in a generally good state of health; he denied a history of tuberculosis or exposure to tuberculosis. He was married and had fathered an in vitro-fertilized

Table 1 Changes in plasma ACTH and cortisol before and after treatment

	ACTH (pg/ml)			Cortisol (ug/dl)		
	8 a.m.	4 p.m.	12 MN	8 a.m.	4 p.m.	12 MN
Base value 1	>1,250	>1,250		8.7	7.16	
Base value 2	>1,250	721.0	405.0	10.2	8.71	7.28
Base value 3	>1,250			14.7		
Small dose dexamethasone suppression test	14.9			1.0		
Large dose dexamethasone suppression test	9.3			<1.0		
Hydrocortisone 20 mg, 8 a.m., oral administration	>1,250	148.0		8.8	10.1	
Hydrocortisone 20 mg, 8 a.m., 10 mg 4 p.m., oral administration	>1,250	33.0		7.3	13.4	
Prednisone 5 mg, oral administration at bed time	180.0	584.0		11.2	7.84	
Dexamethasone 0.75 mg, oral administration at bed time	7.9	7.19		<1.0	<1.0	
Dexamethasone 0.5 mg, oral administration at bed time	6.7	<5.0		<1.0	<1.0	
Dexamethasone 0.375 mg, oral administration at bed time	35.7	8.98		<1.0	<1.0	

Table 2 Results of the ACTH stimulation test

	8 a.m. Blood cortisol (ug/dl)	24 h Urine output (ml)	24 h Urinary free cortisol[a] (ug)
Base value 1	14.6	1450	199.65
Base value 2	11.0	1800	193.75
The first day	10.6	1900	217.32
The second day	11.5	1900	235.39
The third day	8.8	2100	232.24
The fourth day	10.5	1800	206.50
The fifth day	10.9	2300	199.55

[a] Reference range 28.50–213.70 (μg)

female baby. The patient had normal sexual function, but his rate of teratospermia was high; he also denied a familial history of similar diseases (Tables 1 and 2).

Physical examination on hospital admission indicated temperature 36.7°C, respiration 20/min, pulse 80/min, blood pressure 110/80 mmHg, body height 165 cm, and body weight 48 kg. Systematic diffuse skin pigmentation appeared to be brown–black in color, especially obvious in the face, palms, elbows, gingivae, mammary areolae, and perineum. His exterior genitalia and secondary sex characteristics were normal, but his bilateral testicular texture was slightly soft.

After hospital admission, blood routine test and liver function test for this patient revealed normal results; blood glucose was 3.92 mmol/l, potassium 4.35 mmol/l, sodium 140 mmol/l, and chlorine 99 mmol/l. His plasma ACTH remained high, his plasma cortisol was within the normal range, and diurnal rhythms were absent (Table 1). Tumor markers, immunoglobulin, thyroid function, and thyroid peroxidase antibodies (TPOAb) were all normal and antinuclear antibodies (ANA) were negative. His testosterone (T) was 296.0 ng/dl (reference range: 270–1,730 ng/dl), follicle-stimulating hormone (FSH) was 22.1 mIU/ml (reference range: 1.5–14 mIU/ml), and luteinizing hormone (LH) was 9.44 mIU/ml (reference range: 1.4–7.7 mIU/ml). Results for the renin–angiotensin–aldosterone system (RAAS) were: in a supine position, renin activity 14.99 ng/dl/h (reference range: 0–1.23 ng/dl/h), angiotensin II 158.13 pg/ml (reference range: 16.0–64.0 pg/ml), and aldosterone 95.68 pg/ml (reference range: 59.5–173.9 pg/ml); in a vertical position, renin activity 15.30 ng/dl/h (reference range: 0.47–5.28 ng/dl/h), angiotensin II 696.72 pg/ml (reference range: 25–146 pg/ml) and aldosterone 136.11 pg/ml (reference range: 65.8–295.7 pg/ml). Bilateral adrenal type-B ultrasonic and CT scan showed no abnormalities, X-ray film of the chest and lung CT scan all indicated multiple small pulmonary nodules, and a pituitary MRI showed a plump pituitary shape, upper border was convex and unevenly increased T2-weighted signal intensity, without clear nodular foci, indicating pituitary hyperplasia (Fig. 1). To further clarify this diagnosis, an ACTH stimulation test was conducted by adding 25 u ACTH into 50 ml normal saline (NS), administering intravenously via micro-pump for 8 h in each of 5 successive days to observe changes in the plasma cortisol and 24 h urinary free cortisol (Table 2). No evident increase was observed in the plasma cortisol or

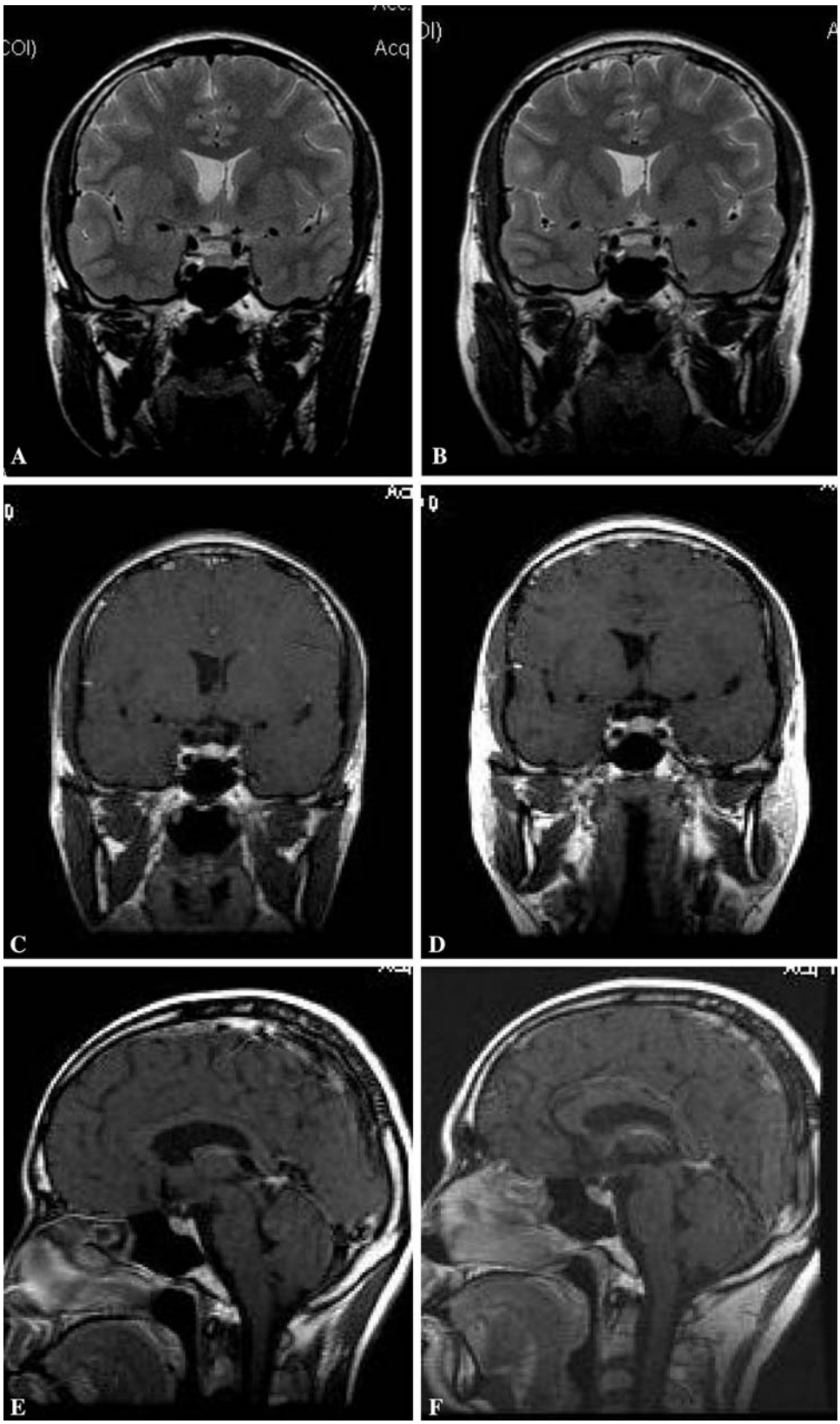

Fig. 1 Pituitary MRI changes before and after glucocorticoid replacement therapy. Coronal T2-weighted images showed a plump pituitary shape, upper border was convex and unevenly increased signal intensity in the adenohypophysial region, especially obvious in the central pituitary region, but without clear nodular foci (**a**); after treatment, a recheck showed no obvious change in the adenohypophysial shape, but there was an even signal intensity and the original irregular high signal intensity had vanished (**b**). Coronal T1-weighted dynamic contrast-enhanced MRI (60 s time phase following G-DTPA injection) showed unevenly intensified adenohypophysis compared with high signal areas of T2-weighted MRI, suggesting increased blood perfusion into local tissues (**c**); a recheck after treatment (the same time point with pre-treatment) showed a uniformly intensified adenohypophysial region (**d**). Sagittal T1-weighted contrast-enhanced MRI (3 min following contrast agent injection) showed uneven intensification of adenohypophysis initially (**e**) and even intensification after treatment (the same time point with pre-treatment) (**f**)

urinary free cortisol following the ACTH drip. To identify hypersecretion of primary or ectopic ACTH, once-through suppression tests with a small dose of 1 mg and a large dose of 8 mg dexamethasone were implemented at midnight, with the result that plasma ACTH and cortisol were significantly inhibited (Table 1). Thus, Addison's disease was

definitively diagnosed. Because hypoadrenocorticism in the patient was not serious, 20 mg hydrocortisone oral replacement therapy was conducted at 8 a.m. each day. One week later, follow-up examination found that plasma ACTH (8 a.m.) was still >1,250 pg/ml, but the value at 4 p.m. was comparatively lower. The daily dose of hydrocortisone was then increased to 30 mg, and ACTH hypersecretion was still not suppressed. Then, 5 mg replacement prednisone was given to the patient at bedtime; the ACTH value declined the next morning, but hypersecretion was still not fully suppressed. Replacing this treatment with dexamethasone (0.75 mg) administered at night, ACTH secretion was fully inhibited; the patient's vigor and appetite were improved, his capacity for eating increased, his trunk skin color began to fade, his body weight increased by 10 kg, and his sanguineous temperament began to occur. Later, the dose of dexamethasone was gradually reduced to 0.375 mg, and plasma ACTH was still controlled through oral administration at bedtime. Six months later during further consultation, the patient's body weight was found to be stable and his skin color had recovered to normal. A pituitary MRI during the follow-up examination showed that pituitary signal intensity had become even and the original irregular signal intensity had vanished (Fig. 1). A recheck of T 224.0 ng/dl, FSH 20.3 mIU/ml, and LH 4.55 mIU/ml showed no significant changes. A recheck of the lung CT scan prompted no evident changes in the shape and density of pulmonary nodules.

Discussion

Diagnosis of Addison's disease is usually not difficult. However, if plasma ACTH is increased, cortisol is normal, and diurnal rhythms absent, this disease must be distinguished from Cushing's disease or ectopic ACTH syndrome. In particular, the patient in this study had multiple pulmonary nodules, so ACTH secretion from a pulmonary tumor had to be excluded. The ACTH stimulation test and dexamethasone suppression test are both helpful for a definite diagnosis. For the patients with Addison's disease, both glucocorticoid and mineralocorticoid are usually deficient. The mineralocorticoid deficiency contributes hypovolemia, resulting in increased concentration and activity of plasma renin. Thus, high renin is helpful to diagnose this disease.

Although ACTH secretion in patients with Addison's disease is excessive, these patients are usually endowed with normal diurnal rhythms [3] and ACTH hypersecretion can be inhibited using glucocorticoid replacement therapy [4]. The blood cortisol levels of patients with partial hypoadrenocorticism can generally be maintained within the normal range. This may result from decreased negative feedback leading pituitary ACTH cell hyperplasia to produce excessive ACTH, stimulating the remnant adrenal cortex to over-secrete cortisol. Long-term ACTH cell hyperplasia may lead to spontaneous ACTH secretion; however, this autonomous function is usually partial. Nodules and even micro-adenomas may develop from ACTH cell hyperplasia, leading to Cushing's disease without hypercortisolism [1, 2, 5–9]. In this situation, cortisol should not be further increased in the ACTH stimulation test. Like the case in this report, 5-day ACTH treatment could not increase cortisol secretion. The diurnal rhythms of plasma ACTH and cortisol disappeared in this patient and ACTH secretion was not inhibited by conventional hydrocortisone replacement therapy, indicating spontaneous ACTH secretion. Small-dose dexamethasone was able to significantly inhibit ACTH secretion, suggesting that this spontaneous secretion was weak. Imaging showed that the pituitary shape was plump, upper border was convex and signal intensity was unevenly increased, but no clear nodular lesions had developed, which also supported the diagnosis of pituitary hyperplasia.

Target organ failure may result in pituitary trophic hormone cell hyperplasia and even the development of adenomas. This phenomenon is frequent in primary hypothyroidism [10, 11], but relatively rare in Addison's disease. Literature reports of surgically confirmed pituitary micro-adenomas secondary to Addison's disease are rare [12]; there are also reports of surgically proven pituitary hyperplasia that were mistakenly regarded as pituitary micro-adenomas [1]. Pituitary imaging is useful for the identification of pituitary hyperplasia and micro-adenomas to some extent, but there are occasional obstacles for distinguishing these features. Hutchins et al. [13] have reported that coronal T1-weighted MRIs of hypothyroidism-induced pituitary hyperplasia show diffuse equal-intensity pituitary enlargement, but Kubota et al. [1] have reported that MRI representations of patients have increased central focal signal intensity and that these high signal areas might contain ACTH dense granules and an excessive density of cell lysosomes. Nevertheless, MRI representations for the majority of ACTH micro-adenomas are low signal foci [14, 15]. This secondary hyperplasia of pituitary cells or micro-adenomas might not need surgical treatment and can mostly be reversed [7].

Secondary pituitary hyperplasia is not only found in patients with Addison's disease who have not been treated for a long time, but also in patients undergoing conventional glucocorticoid replacement therapy. Though these patients originally received daily administration of 30 mg hydrocortisone, the plasma ACTH level in the morning was still elevated. Their skin color did not become shallow. However, these symptoms were alleviated after combined treatment with hydrocortisone and dexamethasone, and

ACTH hypersecretion was inhibited [2]. Thus, the inhibitory effect of a long-acting synthetic glucocorticoid such as dexamethasone or prednisone might be better than that of a short-acting hydrocortisone or cortisone acetate. Because the patient in this study suffered from partial hypocorticalism, hydrocortisone replacement therapy was first attempted, but a daily dose of up to 30 mg still was not able to effectively inhibit ACTH hypersecretion in the morning; later replacement with prednisone also was unable to achieve satisfactory control. Nevertheless, replacement with long-acting dexamethasone was able to fully inhibit ACTH secretion. Morning plasma ACTH concentration should be less than 80 pg/ml [16]. The patient's skin color returned to normal; a recheck of the MRI showed even pituitary signal intensity, with the disappearance of the original irregular high signal intensity indicating alleviated pituitary hyperplasia. Therefore, for patients with Addison's disease accompanied by pituitary hyperplasia or micro-adenomas, it is suggested that replacement therapy using a long-acting glucocorticoid such as dexamethasone can be applied to obtain a full inhibitory effect on ACTH secretion. The pituitary MRI should be observed dynamically to identify the response of the pituitary lesions to replacement therapy to further assist with a definite diagnosis and avoid unnecessary surgical procedures.

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