

Adrenocortical hypofunction with simultaneous primary aldosteronism

A case report

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Abstract

Rationale: Cases of adrenocortical hyperfunction combined with primary aldosteronism have been reported in the literature, and the underlying mechanism involves the secretion of aldosterone and glucocorticoids by a tumor or an adenoma. However, adrenocortical hypofunction and coexisting primary aldosteronism have not been reported until now. Herein, we report a case of adrenocortical hypofunction combined with primary aldosteronism.

Patient concerns: A 66-year-old Chinese woman with rheumatoid arthritis who had been diagnosed with secondary adrenal insufficiency and was taking prednisone acetate tablets for replacement treatment presented to our department. She also had type 2 diabetes mellitus, osteoporosis, bilateral knee osteoarthritis, and lumbar vertebral compression fracture. She had previously developed tuberculosis, which had been cured.

Diagnosis: The cortisol and adrenocorticotropic hormone rhythm indicated cortisol dysfunction in the patient. A 64-slice computed tomography and magnetic resonance imaging both showed bilateral adrenal hyperplasia. A postural stimulation test indicated a high level of aldosteronism and a high aldosterone-to-renin ratio (ARR, supine position: aldosterone 1788.73 pg/mL, ARR 146.62; upright position: aldosterone 2916.21 pg/mL, ARR 92.29). The captopril test showed the aldosterone level decreased by 364.70 pg/mL 1 hour after administration of captopril (from 2153.28 to 1788.58 pg/mL). The decline in aldosterone level was approximately 16.90% (i.e., <30%), and the ARR was still >40. Based on the above-mentioned findings, we diagnosed the patient with adrenocortical hypofunction with primary aldosteronism.

Interventions: We administered spironolactone 20 mg twice daily and continued the glucocorticoid replacement therapy.

Outcomes: One week after diagnosis, the patient had an aldosterone level of 2201.16 pg/mL, plasma renin activity of 3.88 ng/mL/h, and an ARR of 56.7 (upright position). Her blood pressure was maintained within the normal range.

Lessons: Although adrenocortical hypofunction with primary aldosteronism is rare, cases of primary aldosteronism complicated with hypercortisolism are occasionally encountered. Hence, whenever possible, we recommend testing both aldosterone and cortisol levels in all patients with adrenal dysfunction.

Abbreviations: ARR = aldosterone-to-renin ratio, AVS = adrenal venous sampling, CT = computed tomography, MRI = magnetic resonance imaging.

Keywords: adenoma, adrenal, aldosteronism, cortical hypofunction, diabetes

1. Introduction

Cases of adrenocortical hyperfunction combined with primary aldosteronism have been previously reported. The underlying

mechanism mainly involves the secretion of aldosterone and glucocorticoids by a tumor or an adenoma.^[1–3] However, the coexistence of adrenocortical hypofunction and primary aldosteronism has not yet been reported.

Herein, we report a case of adrenocortical hypofunction combined with primary aldosteronism, which may be the 1st case reported in the literature in the world.

2. Case report

A 66-year-old retired Chinese woman visited our department because of joint pain for 1 week. The patient had rheumatoid arthritis for over 10 years. After being diagnosed with secondary adrenal insufficiency 2 years ago, she had been regularly taking prednisone acetate tablets 5 mg in the morning and 2.5 mg in the afternoon for replacement treatment. She was diagnosed with type 2 diabetes mellitus 8 years ago and is currently administered insulin “aspartate 30” at a dosage of 30 units per day. Her blood sugar control was acceptable. She had tuberculosis 6 years ago, which has been cured. She had been diagnosed with osteoporosis, bilateral knee osteoarthritis, and lumbar vertebral compression fracture 3 years ago. She had no history of hypertension or

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Table 1**Cortisol and adrenocorticotropic hormone rhythm.**

	8:00 AM	4:00 PM	0:00 AM
ACTH, pmol/L Ref: 1.6–13.9	<0.22	0.24	<0.22
Cortisol, nmol/L Ref: (7–10 AM) 133–537 (4–8 PM) 68.2–327	29.85	53.21	51.20

ACTH = adrenocorticotropic hormone.

episodes of hypokalemia. She had no abnormal signs in her general appearance. The patient provided written informed consent for the publication of this case report and the related figures in accordance with the Declaration of Helsinki.

After admission, the patient's hepatic and renal function, tumor markers, anti-streptolysin O, rheumatoid factor, thyroid function, c-reactive protein level, and sex hormone levels were normal. Her routine blood analysis was as follows: white blood cell count, $13.17 \times 10^9/L$; hemoglobin level, 97 g/L; platelet count, $196 \times 10^9/L$; and erythrocyte sedimentation rate, 108 mm/h. The urine routine was normal (urinary specific gravity, 1.007; urine pH, 7.0). The initial electrolyte levels were as follows: potassium, 3.83 mmol/L; sodium, 144.60 mmol/L; and chlorine, 108.90 mmol/L. The electrolyte levels during the 1-week review were as follows: potassium, 3.84 mmol/L; sodium, 144.26 mmol/L; and chlorine, 109.81 mmol/L, which suggested a slight increase in chlorine, normal upper limit of sodium, and normal lower limit of potassium.

There were no abnormal findings in the electrocardiogram and B-mode ultrasonography. Previous pulmonary tuberculosis in the left upper lobe and fracture in the 3rd anterior rib on the right side were observed using chest computed tomography (CT). The cortisol and adrenocorticotropic hormone rhythm supporting cortisol dysfunction is shown in Table 1.

Considering the long-term cortisol dysfunction in the patient, we arranged a 64-slice CT test to evaluate the presence of adrenal

Table 2**Postural stimulation test results.**

	Supine position	Upright position	Reference
Angiotensin I 37°C, ng/mL	1.54	4.07	
Angiotensin I 4°C, ng/mL	0.32	0.91	
Plasma renin activity, ng/mL/h	1.22	3.16	Erect: 1.31–3.95 Supine: 0.15–2.33
Aldosterone, pg/mL	1788.73	2916.21	Upright: 40–310 Supine: 10–160
Ratio of aldosterone-to-renin activity	146.62	92.29	

gland atrophy. We observed bilateral adrenal hyperplasia (Fig. 1A). This finding was unexpected, and therefore, we completed the postural stimulation test and further investigated the adrenal and pituitary glands using magnetic resonance imaging (MRI). The MRI showed pituitary microadenomas (0.5×0.4 cm) and bilateral slightly thicker adrenal glands (Fig. 1B). In the postural stimulation test, the aldosterone level increased significantly, but the renin level was not as high, and therefore, the aldosterone-to-renin ratio (ARR) was obviously abnormal (Table 2).

Due to the absence of an ambulatory blood pressure monitor, repeated manual measurements of blood pressure were recorded every 2 hours. Her blood pressure fluctuated from 110 to 130/70 to 80 mm Hg. We further completed the captopril test,^[4] and the aldosterone level decreased by 364.70 pg/mL 1 hour after administration. The decline in aldosterone level was approximately 16.90% (i.e., <30%), and the ARR was >40,^[4] which indicates aldosteronism (Table 3).

The test for renin-aldosterone using the chemiluminescence method was commissioned by a qualified laboratory. Based on previous studies,^[5,6] the chemiluminescence assay and radioimmunoassay are highly correlated and can be used to detect accurate aldosterone levels.

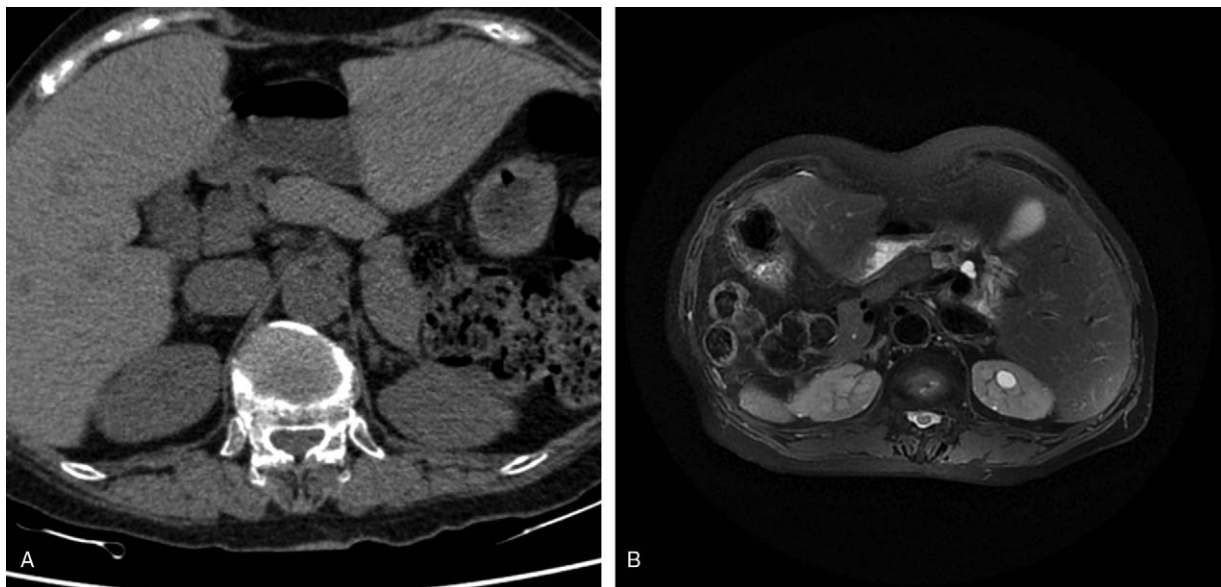


Figure 1. A 64-slice (A) computed tomography and (B) magnetic resonance imaging both showed bilateral adrenal hyperplasia.

Table 3**Captopril (25 mg) test.**

Renin activity	7:30 AM (supine) Before administration	9:30 AM (sitting position) Before administration	10:30 AM (sitting position) 1 h after administration
Angiotensin I (4°C) A1, ng/mL	0.50	0.70	0.56
Angiotensin I (37°C) A1, ng/mL	2.65	4.53	4.37
Plasma renin activity, ng/mL/h Ref: (erect 1.31–3.95; Supine, 0.15–2.33)	2.15	3.83	3.81
Aldosterone, pg/mL Ref: (upright 40–310; Supine, 10–160)	1483	2153.28	1788.58
Ratio of aldosterone-to-renin activity	68.98	56.22	46.94

We asked for the laboratory to repeatedly verify our results and test stability, and they guaranteed that their reagents and instruments are qualified for use.

The accuracy of the method for renin-aldosterone test was also verified when we used it in another patient, who was diagnosed with multiple adenocarcinoma (a large growth hormone-secreting pituitary adenoma combined with aldosteronoma) with an aldosterone level of >1000 pg/mL during the same period. This patient's electrolytes were normal, but her blood pressure was moderately elevated, supporting the diagnosis.

The patient had a tendency for low potassium and high sodium levels, and both MRI and CT findings indicated mild adrenal hyperplasia. The diagnosis of adrenocortical hypofunction combined with primary aldosteronism was established by combining the findings regarding the aldosterone level and captopril test findings. Idiopathic aldosteronism is the likely subtype of primary aldosteronism in this patient.

Considering that the patient is usually free from discomfort, the electrolyte levels and other internal environment factors were stable. We administered 20 mg of spironolactone twice daily to the patient to reduce potential discomfort associated with electrolyte changes.

One week after diagnosis, the patient was evaluated and reviewed. The following results were obtained (upright position): aldosterone, 2201.16 pg/mL; plasma renin activity, 3.88 ng/mL/h; and ratio of ARR, 56.70. The aldosterone level decreased by 715.00 pg/mL after spironolactone administration (2916.21 pg/mL), indicating that the spironolactone's effect was better than captopril's effect. It was clear that the treatment of spironolactone was effective and simultaneously; her blood pressure was maintained in the normal range at 130/72 mm Hg.

We recommend the patient further check the adrenal venous sampling,^[4] radioimmunoassay measurements,^[7] and radioactive iodine cholesterol scan.^[8] However, there were no such technology in our region, and the patient was not willing to undergo further diagnostic testing at other hospitals for economic reasons.

3. Discussion

The patient's medical history, symptoms, signs, and examination results did not support the loss of sodium nephropathy, pseudo aldosterone deficiency, renal tubular acidosis, Bartter syndrome, Liddle syndrome, renin tumor, and other diseases. No tumors were identified and the patient had been receiving glucocorticoid replacement therapy which excluded the effect of cortisol dysfunction on our results,^[9] and the patient was not taking

other drugs, such as antihypertensive drugs, metoprolol, and spironolactone; therefore, the effects of drugs can be ruled out.

This was the 1st case of adrenocortical hypofunction combined with primary aldosteronism. However, there are several doubts about the clinical manifestations and index of this patient. Firstly, the patient's aldosterone level was very high, but the adrenal glands had only mild hyperplasia. A possible cause for this was that the long-term secondary adrenal hypofunction tends to cause adrenal gland atrophy.^[9] The imaging morphology may appear as mild hyperplasia or near normal because the idiopathic aldosteronism had been offset by adrenal hyperplasia.^[10]

Secondly, although the aldosterone level was very high, the changes in symptoms, signs, and results were not obvious at all. The patient only showed a trend of low potassium and high sodium levels, and the repeated measurements of blood pressure were normal. These findings were incongruent with current perceptions. The underlying mechanisms are hypothesized below. Firstly, *in vivo* gene mutations lead to abnormal aldosterone receptors in aldosterone resistance, similar to insulin resistance,^[11] requiring higher levels of aldosterone to maintain physiologic function. Secondly, aldosterone antibodies, similar to insulin antibodies,^[12] also inhibit the function of aldosterone. Lastly, it could be due to an aldosterone structural abnormality. The aldosterone chemical formula *in vivo* is C₂₁H₂₈O₅, and the chemical structure is (11β)-11,21-dihydroxy-3,20-dioxopregn-4-en-18-al.^[13] It is possible that there are other structures that have weak physiologic function or are nonfunctional. Furthermore, the current monitoring chemiluminescence method cannot distinguish between normal and abnormal aldosterone^[7] and, therefore, the physiologic activity was not strong despite a high aldosterone level.

The present case has some limitations. First, we could not conduct adrenal tissue biopsy, bilateral adrenal venous blood sampling to assist the diagnosis and identification of primary aldosteronoma or idiopathic aldosteronism, and complete positron emission imaging for excluding tumors. Furthermore, radioimmunoassay, which may provide more data, has been discontinued in many domestic hospitals or 3rd-party testing institutions due to the complicated procedures and issues related to radioactivity.

Therefore, bilateral adrenal venous blood sampling, radioimmunoassay and adrenal tissue biopsy are the next steps to explore more additional evidence.^[10]

We also hope that another institution capable of identifying chemical structures can help us determine whether the aldosterone in this patient has an abnormal structure to enhance our understanding of this rare and world's 1st case.

Although adrenocortical hypofunction with primary aldosteronism is rare, cases of primary aldosteronism complicated with hypercortisolemia are occasionally encountered.^[1] Hence, whenever possible, we recommend testing both aldosterone and cortisol levels in all patients with adrenal dysfunction.

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