ADRENAL ADENOMA WITH AUTONOMOUS CORTISOL SECRETION ACCOMPANIED BY HOMOLATERAL RENAL CELL CARCINOMA: A CASE REPORT

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Abstract

Context. Patients with renal malignancies present high risk of adrenal hyperplasia and adenoma, and part of these are primary lesions, mostly non-functional. Here we presented a case diagnosed as primary adrenal adenoma with autonomous cortisol secretion accompanied by homolateral renal cell carcinoma.

Case presentation. A 79-year-old woman was referred for evaluation of a left adrenal mass, with a past medical history of severe hypertension, diabetes, and hyperlipidemia. On examination, no clinical signs of cushingoid features were found. Biochemical measurements showed plasma cortisol was 12.77 µg/dL and was not suppressed by 1 mg dexamethasone (DXM) overnight test (13.6 µg/dL). The contrast CT scan presented a 2.2 cm diameter adrenal mass and revealed, unfortunately, a hyperdense mass at the middle-upper pole of the left kidney. Laparoscopic nephrectomy with left adrenalectomy was performed and pathological examination indicated a final diagnosis of benign adrenocortical adenoma and renal clear cell carcinoma. At 2 months postoperatively, without replacement treatment of cortisol, a recovery of circadian rhythm of cortisol secretion was detected, indicated recovery of the hypothalamic-pituitary-adrenal axis.

Conclusions. Patients with renal cancer might be accompanied with functional adrenal adenoma. Therefore, screening for adrenal function should be recommended in patients with renal tumors and/or adrenal incidentaloma.

Key words: Subclinical Cushing's syndrome, renal carcinoma, adrenal adenoma, adrenal incidentaloma.

adults is 0.2-2%, mainly from patients with adrenal incidentaloma (AI)(1). As reported, about 5%-20% of patients with AI have autonomous cortisol secretion (2). Based on a latest report, the prevalence of autonomous cortisol secretion in AI patients could be as high as 50% (3). Without typical appearances of Cushing's syndrome, the confirmation of autonomous cortisol secretion in these patients is mainly relied on dexamethasone test. However, this overproduction of cortisol by adrenal mass is still related to abnormal glucose tolerance, hyperlipidemia, hypertension and other metabolic complications in these patients (4). Several studies have reported that patients with a variety of malignancies are prone to occurring adrenal hyperplasia as compared to normal patients (5,6). This is due to primary lesion rather than metastases, and probably associated with disturbed pituitary-adrenal regulation in some patients (7). However, there are few reports of simultaneous occurrence of adenoma with autonomous cortisol secretion and renal carcinoma. Ermanno *et al.* have reported a case of combined Conn's Syndrome and SCS due to an aldosterone cortisol-producing adenomas with homolateral renal carcinoma but no significant metabolic complications of SCS were discovered in that patient (8). In this regard, here we described a case of adrenal functional adenoma manifested in autonomous cortisol secretion with severe hypertension, diabetes, hyperlipidemia and osteoporosis accompanied by homolateral renal carcinoma.

INTRODUCTION

Patients with "autonomous cortisol secretion", formerly called "Subclinical Cushing's syndrome (SCS)" is referred to the condition of low-level autonomous cortisol secretion in patients who are deprived of typical manifestations of hypercortisolism. The incidence of autonomous cortisol secretion in

CASE PRESENTATION

A 79-year-old woman was referred to the endocrine clinic for evaluation of a left adrenal mass that was discovered by computed tomography (CT) scan. This adrenal mass with a diameter of 2.0 cm was accidentally found by a chest CT scan and appeared

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round shaped and low-density with -11 Hounsfield units on the non-contrast scan. The decision was made not to remove the tumor at that time. She underwent a follow-up chest CT scan 6 months after last check-up, which revealed that the diameter of adrenal mass had enlarged to 2.5 cm. Her past medical history was remarkable for a severe hypertension despite being prescribed multiple anti-hypertensives. Though the patient denied a history of diabetes, a high glycosylated hemoglobin (6.8%) was detected six months ago. She also received statin treatment for hyperlipidemia.

The patient was normal weight (BMI 23.42 kg/m²) and had moderate arterial hypertension (166/90 mmHg) on admission. No clinical signs of overt hypercortisolism were found at physical examination. In particular, she lacked cushingoid features such as moon-shaped face, purple striae, centripetal obesity, supraclavicular fat pad accumulation and buffalo hump, proximal weakness or plethora.

Laboratory measurements showed normal creatinine but an altered lipid profile (Table 1). Results from OGTT indicated a high postprandial glucose (over 11.1 mmol/L) confirming the diagnosis of diabetes.

Plasma aldosterone (12.4 ng/dL), plasma renin activity (1.18 ng/mL/h), and total urinary nephtrins were all normal. A relative low level of plasma DHEA-S (0.35 umol/mL, reference range: 0.33-4.18 umol/mL) was detected and the circadian rhythm of cortisol secretion has disappeared in this patient. Urinary free cortisol excretion was 71.83 ug/24 hours reference range: 28.50-213.70 ug/24 hours, while plasma cortisol and adrenocorticotrophic hormone (ACTH) was 12.77 µg/dL and 3.43 pg/mL respectively and plasma cortisol was not suppressed by overnight 1mg dexamethasone test (DST) (13.6 µg/dL). A bone mineral density test revealed osteoporosis (lumbar total T score: 1.1; femoral neck T score: -3.1). The contrast CT scan of adrenal gland presented a 2.2 cm diameter adrenal mass with -16 Hounsfield units on the non-contrast scan but 20-30 Hounsfield units after contrast and revealed, unfortunately, a hyperdense mass 3.0 × 3.2cm in diameter at the middle-upper pole of the left kidney (Fig. 1).

Our present data were in support of a diagnosis of autonomous cortisol secretion due to a left adrenal mass with an unexpected renal lesion. After consultation

Table 1. Preoperative and postoperative laboratory data

Laboratory parameters	Baseline	1 st day after surgery	3 rd day after surgery	2 nd month after surgery	Reference range
p[creatinine](µmol/L)	63.9	148.5	253.1	158.8	35.0-71.0
BUN (mmol/L)	4.53	6.42	11.43	11.85	2.90-7.10
p[K ⁺] (mmol/L)	3.57	3.19	3.97	4.00	3.50-5.30
p[Na ⁺] (mmol/L)	142	138	136	141	137-147
CO ₂ -CP	28.1	27.1	25.4	28.9	22.0-29.0
FBG (mmol/L)	6.35	-	-	7.09	3.90-6.10
2hPG (mmol/L)	13.29	-	-	-	<7.8
HbA1c	7.0%	-	-	-	4.0-6.0
p[triglyceride] (mmol/L)	1.59	-	-	2.79	0.56-1.47
p[cholesterol] (mmol/L)	5.45	-	-	6.45	3.10-5.69
LDL-c (mmol/L)	3.29	-	-	4.51	<3.1
p[aldosterone] (ng/dL)	124.45	-	-	-	40-310
PRA (µg/L/h)	1.18	-	-	-	4-38
ARR	105.46	-	-	-	
NMN(pg/mL)	111	-	-	-	<145
MN(pg/mL)	16.5	-	-	-	<62
Baseline[cortisol](µg/dL)	12.77	-	-	15.56	4.26-24.85
Baseline[ACTH] (pg/mL)	7.51	-	-	100	7.20-63.40
4pm [cortisol] (µg/dL)	13.20	-	-	3.89	2.9-17.3
4pm [ACTH] (pg/mL)	4.42	-	-	28	7.20-63.40
Midnight[cortisol](µg/dL)	12.90	-	-	3.27	2.9-17.3
Midnight[ACTH](pg/mL)	3.96	-	-	24	7.20-63.40
p[cortisol], post-overnight 1mg DXM (µg/dL)	13.61	-	-	-	
24h UFF (µg/24 h)	71.83	-	-	104.90	28.50-213.70
DHEAS (umol/L)	0.35	-	-	-	0.33-4.18

Baseline PRA, p[aldosterone], p[ACTH] and p[cortisol] were obtained at 8 AM after 1 h quiet rest in the sitting position. ARR, Aldosterone to PRA ratio; NMN, Normetanephrene; MN, Metanephrene ACTH, adrenocorticotrophic hormone; BUN, blood urea nitrogen; p, plasma; FBG, fasting blood glucose; 2hPG, 2h postprandial glucose; PRA, plasma renin activity; UFF, urinary-free cortisol; DXM, dexamethasone; DHEAS, dehydroepiandrosteronesulfate.

Figure 1. Scan of adrenal and renal lesions by Computed tomography (A,B - Non-contrast; C,D-Contrast). (A) Left adrenal mass (arrows), 2.2 cm in diameter, with homogeneous low density; (B) Renal mass at middle-upper pole of the left kidney (arrowheads), 3.0 cm in diameter, with homogeneous high density; (C) Contrast scan showed a mild enhancement of adrenal lesion with 20-30HU; (D) Contrast scan of renal mass in arterial phase showed a heterogeneous grid-like enhancement.

with urologists and discussion with the patient, left nephrectomy with left adrenalectomy was performed by laparoscopic surgery. Hydrocortisone (200 mg to 100 mg per day) was intravenously administered in the first 3 days after operation, and then discontinued. Three days after surgery, no complaint of symptoms of adrenal insufficiency such as weakness, anorexia, nausea, abdominal pain, or postural dizziness were heard from this patient. Her blood pressure was 140/90 mmHg under control of three antihypertensive drugs (Nifedipine 30mg qd, Irbesartan 150 mg qd, Terazosin 2 mg qd). Laboratory examinations showed hyponatremia, an increase of creatinine and a decrease in renal glomerular filtration rate (GFR). No further oral hydrocortisone was prescribed for her then. Histological examination indicated a final diagnosis of benign adrenocortical adenoma and renal clear cell carcinoma (Fig. 2).

At the last clinical examination, 2 months postoperatively, without cortisol replacement treatment, a recovery of circadian rhythm of cortisol secretion was detected. Serum sodium concentration was normalized, but no notable improvement of hyperlipemia and hyperglycemia compared to those found preoperatively. Blood pressure was still 140/90 mmHg under control of three antihypertensive drugs (Nifedipine 30mg qd, Irbesartan 150 mg qd, Terazosin 2 mg qd). This patient is still under follow-up.

DISCUSSION

Here we presented a patient with autonomous cortisol secretion due to adrenal incidentaloma accompanied by renal carcinoma. Adrenal gland is a common metastatic site of renal malignancy. When the two lesions coexist, renal carcinoma with adrenal

Figure 2. Histological analysis of adrenal and renal lesions. (A) Left clear cell renal cell carcinoma: large and uniform nuclei with open chromatin; (B) CD10 positive cells were discovered in tumor tissue; (C) EMA positive cells were discovered in tumor tissue; (D) Left adrenal adenoma: large, polygonal, clear cells admixed with focal areas of compact, eosinophilic cells. (E) Inhibin positive cells were discovered in adrenal adenoma; (F) Melan A positive cells were discovered in adrenal adenoma.

metastasis is firstly under consideration. Among the current reports on adrenal incidentaloma coexisted with malignancies, nearly half part of these AIs could be manifested by primary adrenal mass, mostly non-functional (9,10). Only sporadic cases have been reported with functional adenoma (8). However, after evaluation of adrenal hormones in this patient, we detected a disturbed circadian rhythm of cortisol secretion which was not inhibited by overnight 1 mg

DST indicating autonomous-secretion. Pathology suggested primary adrenal adenoma with clear cell renal carcinoma in this patient, which further confirmed our conclusion.

Autonomous cortisol secretion is defined as a condition that has abnormal secretion of cortisol hormone but lacks clinical manifestations of Cushing's syndrome which distinguished from overt Cushing's syndrome (11). Due to the absence of

typical appearances, this abnormal condition is often overlooked. Dexamethasone suppression test is a reliable diagnostic basis. Most guidelines recommend 1mg overnight DST as a universal test for diagnosis of autonomous cortisol secretion (12,13), and cortisol levels post dexamethasone >138 nmol/L (>5.0 $\mu\text{g/dL}$) should be taken as evidence of “autonomous cortisol secretion” based on ESE guideline (14). In this patient, we followed the rules of that cortisol concentration <1.8 $\mu\text{g/dL}$ (183nmol/L) after 1mg DST was excluded, while cortisol concentration >5.0 $\mu\text{g/dL}$ after 1mg DST was confirmed. However, owing to the autonomous production of cortisol by adrenal mass, patients with SCS also tend to develop the metabolic disorders of overt Cushing’s syndrome, including abnormal glucose tolerance, abnormal lipid metabolism, hypertension, osteoporosis and so on. Moreover, for patients already with diabetes, hypertension, or hyperlipidemia, this abnormal increase in cortisol secretion may lead to the aggravation of primary diseases, increase the progression of cardiovascular and cerebrovascular diseases and the risk of mortality (15,16). In this patient, a severe hypertension, diabetes and hyperlipidemia had already existed before discovery of AI and bone density test also indicated the existence of osteoporosis, which further complicated the situation of SCS in the patient.

There is currently no consensus on the treatment of adrenal incidentaloma presenting as SCS. A prospective randomized study on evaluating the efficacy of surgical and conservative management in AI patients presenting with SCS found that cortisol secretion from adrenal cortex all recovered in 23 patients undergoing surgical treatment. Following 15-year postoperative follow-up, DM was normalized or ameliorated in 62.5% of patients (5 of 8), hypertension in 67% (12 of 18), hyperlipidemia in 37.5% (3 of 8), and obesity in 50% (3 of 6) in the surgical group. No patients progressed to overt Cushing’s syndrome in non-operative management group at end of follow-up, but some patients had turned to the surgical therapy because of progressive growth of adrenal mass (>3.5 cm), and some patients showed worsening of diabetes and high blood pressure (17). For our patient, surgical treatment was also the first choice due to the combination of a left renal mass. Moreover, two months after the operation, the function of adrenal cortisol secretion was re-evaluated, patients’ cortisol circadian rhythm was restored, and the ACTH level was increased at 8 am, suggesting recovery of adrenal cortisol secretion. Although no significant improvements

in diabetes, hypertension, or hyperlipidemia were observed in our follow-up two months after surgery, it may be owing to the short follow-up time. A recent prospective randomized study also reported that results from domestic 48 SCS patients undergoing surgical treatment due to AI indicated improvement of blood pressure, glycosylated hemoglobin and triglyceride levels. No obvious improvement in levels of blood pressure, glycosylated hemoglobin and triglycerides were observed in the conservative treatment group while given oral drugs in the control of diabetes, hypertension, or hyperlipidemia at the end of follow-up (18). Therefore, surgical treatment is still the preferred approach for patients with functional AI presenting as cortisol excess, especially those with a large mass size and risk factors of cardiovascular and cerebrovascular diseases (hypertension, diabetes, hyperlipidemia, etc.).

Patients with oncologic history, particularly lung cancer, breast cancer, and melanoma are at the greatest risk of adrenal disease (6). Studies also showed that the risk of adrenal hyperplasia and adenoma in patients with renal cancer is 3–4 times of that in normal people but the majority are primary lesions, and usually non-functional (10). However, the connection between adrenal functional lesions and extra-adrenal malignancies has not been fully investigated. A recent study has discovered that patients coexisted with extra-adrenal malignancies and adrenal lesions had a similar rate of SH compared to patients with primary adrenal mass but the specific mechanisms were still blurred (19). A recent study also discovered that an overexpression of CYP17 and CYP11B1, which are steroidogenic enzymes, might contribute to cortisol overproduction in patients with SCS due to adrenal adenomas (20). Therefore, whether genetic factors are involved in the pathogenesis of these conditions remains to be further studied.

In conclusion, here we presented a case diagnosed as adrenal adenoma with autonomous cortisol secretion accompanied by a left renal clear cell carcinoma. As discussed, an assessment of the pituitary–adrenal axis should be commonly performed in patients with AI. Patients with renal cancer are at risk of developing adrenal hyperplasia and adenoma though the underlying mechanisms are still blurred. Therefore, further studies might focus on the pathogenesis of these conditions.

Conflict of interest

All authors have read and approved the final manuscript. No competing interests were declared by all authors.

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