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Editorial Board Member of *World Journal of Clinical Cases*, Dr. Antonio Corvino is a PhD in the Motor Science and Wellness Department at University of Naples "Parthenope". In 2008, he obtained his MD degree from the School of Medicine, Second University of Naples. Then, he completed a residency in Radiology in 2014 at University Federico II of Naples. In 2015, he undertook post-graduate training at Catholic University of Rome, obtaining the 2nd level Master's degree in "Internal Ultrasound Diagnostic and Echo-Guided Therapies". In 2016-2018, he served on the directive board of Young Directive of Italian Society of Ultrasound in Medicine and Biology. His ongoing research interests involve ultrasound and ultrasound contrast media in abdominal and non-abdominal applications, etc. (L-Editor: Filipodia)

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Primary aldosteronism due to bilateral micronodular hyperplasia and concomitant subclinical Cushing's syndrome: A case report

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Abstract

BACKGROUND

Adrenal incidentaloma (AI) has been frequently encountered in the clinical setting. It has been shown that primary aldosteronism (PA) or subclinical Cushing's syndrome (SCS) are the representative causative diseases of AI. However, the coexistence of PA and SCS has been reportedly observed. Recently, we encountered a case of AI, in which PA and SCS coexisted, confirmed by histopathological examinations after a laparoscopic adrenalectomy. We believe that there were some clinical implications in the diagnosis of the present case.

CASE SUMMARY

A 58-year-old man presented with lower right abdominal pain with a blood pressure of 170/100 mmHg. A subsequent computed tomography scan revealed right ureterolithiasis, which was the cause of right abdominal pain, and right AI measuring 22 mm × 25 mm. After the disappearance of right abdominal pain, subsequent endocrinological examinations were performed. Aldosterone-related evaluations, including adrenal venous sampling, revealed the presence of bilateral PA. In addition, several cortisol-related evaluations showed the presence of SCS on the right adrenal adenoma. A laparoscopic right adrenalectomy was then performed. The histopathological examination of the resected right adrenal revealed the presence of a cortisol-producing adenoma, while CYP11B2 immunoreactivity was absent in this adenoma. However, in the adjacent non-

conflict of interest.

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neoplastic adrenal, multiple CYP11B2-positive adrenocortical micronodules were detected, showing the presence of aldosterone-producing adrenocortical micronodules.

CONCLUSION

Careful clinical and pathological examination should be performed when a patient harboring AI presents with concomitant SCS and PA.

Key Words: Primary aldosteronism; Subclinical Cushing's syndrome; Adrenal incidentaloma; Micronodular hyperplasia; Case report

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Core Tip: Adrenal incidentaloma (AI) has been frequently encountered in the clinical setting. It has been shown that primary aldosteronism (PA) or subclinical Cushing's syndrome (SCS) are the representative causative diseases of AI. However, the coexistence of PA and SCS has been reportedly observed. In the present case report, we describe a case of AI, in which PA and SCS coexisted after endocrinologic examinations, which was ultimately confirmed by histopathological examinations after a laparoscopic adrenalectomy. Careful clinical examinations should be performed when patients harboring AI present with concomitant SCS and PA.

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INTRODUCTION

Adrenal incidentaloma (AI) has been frequently encountered in the daily clinical practice. The concomitant clinical presentation of subclinical Cushing's syndrome (SCS) and/or primary aldosteronism (PA) in patients with AI is not necessarily rare. However, the rate of those patients among AI cases also depends on the lesion's laterality and size, the presence of hypertension, and gender^[1-4]. Conversely, among hypertensive patients, the prevalence of PA was recently reported to be relatively higher, in the range of 5%-10%^[5,6]. Among those patients described above, the coexistence of SCS and PA has also been reported to range from 11.3% to 53.8%^[7-10], and careful clinical evaluation is required to identify those patients harboring SCS and PA. We recently encountered a case with concomitant manifestation of bilateral PA and SCS in the right adrenal gland confirmed by detailed histopathological examination. In view of these findings, this case should provide clinically important information regarding the approach to AI patients harboring these two different endocrine symptoms.

CASE PRESENTATION

Chief complaints

A 58-year-old man visited our outpatient clinic in September 2018 because of a sudden development of lower right abdominal pain, which occurred one hour previously.

History of present illness

He reported lower right abdominal pain that had continued for one hour at the same degree and in the same portion.

History of past illness

He had no prior contributory medical history, although no health checkups had been

performed.

Personal and family history

He had no obvious family history of the disease.

Physical examination

The results of his physical examination were as follows: height, 1.75 m; weight, 79.4 kg; body mass index, 25.9 kg/m²; blood pressure, 170/100 mmHg (systolic/diastolic); and pulse rate, 76 beats/min. No cardiac murmur nor abnormal respiratory sounds were noted, and he complained of knocking pain in his right back. There was no tenderness on his abdomen, with normal body shape and no particular dermal findings.

Laboratory examinations

Routine laboratory examination revealed a reduced estimated glomerular filtration rate (45.8 mL/min/1.73 m²) with normal potassium levels (4.5 mEq/L). The patient's fasting blood glucose level was 87 mg/dL, with hemoglobin A1C of 6.0%.

Imaging examinations

An electrocardiogram demonstrated regular sinus rhythm without any evidence of left ventricular hypertrophy (LVH) and an echocardiography showed normal left ventricular wall motion and no indications for LVH. Subsequent computed tomography (CT) performed for exploration of his abdominal pain revealed the presence of a right ureterolithiasis, which could account for his symptoms, and a right adrenal adenoma measuring 22 mm × 25 mm (Figure 1).

Further diagnostic work-up

The patient was subsequently treated with analgesic drugs to control his pain due to the right ureterolithiasis, and the stones were excreted after a few weeks.

While his hypertension had been treated with a calcium channel blocker with amlodipine (10 mg), detailed examination on his right AI was also performed for the possible presence of pheochromocytoma, PA, and SCS. The urinary metanephrines were within the normal range. Magnetic resonance imaging revealed the presence of a right adrenal tumor (Figure 2), as detected in CT. The salt loading test was positive, with a plasma aldosterone concentration (PAC) of 83 pg/mL, consistent with PA. However, the captopril challenge test was negative, and the aldosterone/renin ratio (ARR) after the challenge was in the range of 192.5 (< 200). The subsequent adrenal venous sampling (AVS) revealed bilateral increase of plasma aldosterone levels following intravenous infusion of adrenocorticotrophic hormone (ACTH) (aldosterone: 15251 pg/mL in the right adrenal vein, 14.271 pg/mL in the left adrenal vein; cortisol: 618.1 µg/dL in the right adrenal vein, 530.5 µg/dL in the left adrenal vein, and a lateralized ratio 1.09), with a higher increase in the aldosterone level in the left adrenal gland before ACTH infusion (Table 1). Based on these findings, we ultimately diagnosed this patient as bilateral PA. In addition, dexamethasone administrations (1 or 8 mg) did not suppress the production of cortisol (cortisol: 4.5 µg/dL in 1 mg dexamethasone; 3.3 µg/dL in 8 mg dexamethasone). ACTH and cortisol concentrations in the early morning were 2.4 pg/mL and 5.9 µg/dL, respectively. Conversely, the concentration of cortisol at midnight was 4.6 µg/dL. These findings all indicated the presence of diurnal variation in cortisol patterns. In addition, an increased ACTH concentration was noted in the corticotropin-releasing hormone (CRH) challenge test. Adrenal scintigraphy revealed an increased uptake in the right adrenal gland with its decreased uptake in the left adrenal gland (Figure 3).

FINAL DIAGNOSIS

These findings above all indicated the presence of SCS in this patient. He was therefore diagnosed with concomitant bilateral PA and right SCS.

TREATMENT

His treatment included the administration of the combination of three antihypertensive drugs, including amlodipine (10 mg), eplerenone (50 mg), and

Table 1 Results of adrenal venous sampling

At baseline	Right adrenal vein	Left adrenal vein	Inferior vena cava
Aldosterone (pg/mL)	971	1562	99
Cortisol (μg/dL)	75.9	35.6	6.3
Aldosterone/Cortisol	1.27	4.39	
Laterized ratio (L/R)	3.43		
After ACTH infusion	Right adrenal vein	Left adrenal vein	Inferior vena cava
Aldosterone (pg/mL)	15251	14271	166
Cortisol (μg/dL)	618.1	530.5	16.1
Aldosterone/Cortisol	2.47	2.69	
Laterized ratio (L/R)	1.09		

ACTH: Adrenocorticotrophic hormone.

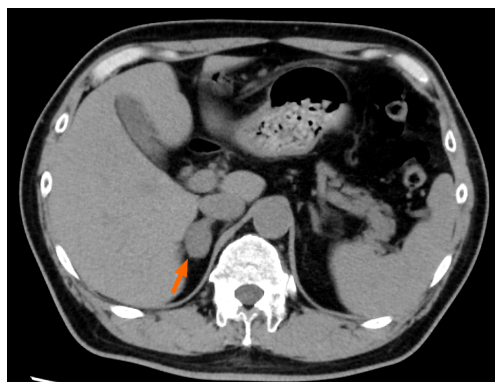


Figure 1 Computed tomography at admission showing a right ureterolithiasis and a right adrenal adenoma with a size of 22 mm × 25 mm (arrow).

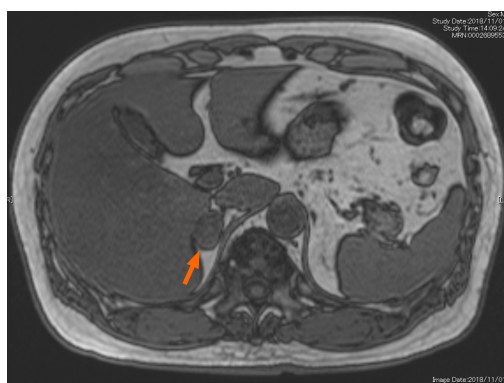


Figure 2 Magnetic resonance imaging showing a right adrenal adenoma with a size of 19 mm × 25 mm × 22 mm (arrow).

bisoprolol (5 mg). A laparoscopic right adrenalectomy was subsequently performed in February 2019 to remove the source of cortisol excess.

OUTCOME AND FOLLOW-UP

An adrenal tumor measuring 2.5 cm × 2.3 cm × 2.0 cm (Figure 4A) was detected in the resected right adrenal gland. The cut surface of the tumor appeared heterogeneous,

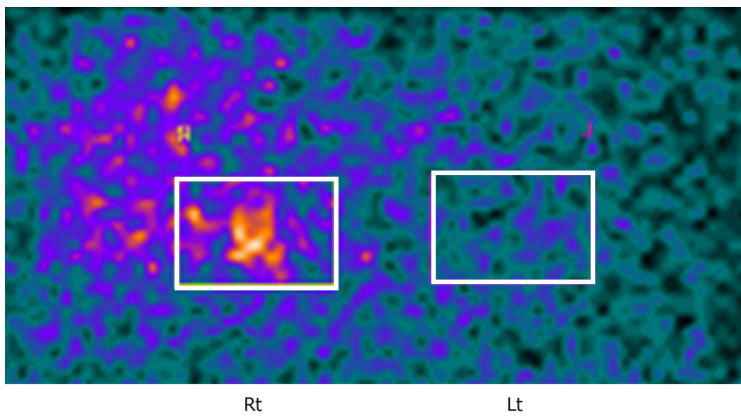


Figure 3 Adrenal scintigraphy demonstrated the increased uptake in the right adrenal gland and the decreased uptake in the left adrenal gland.

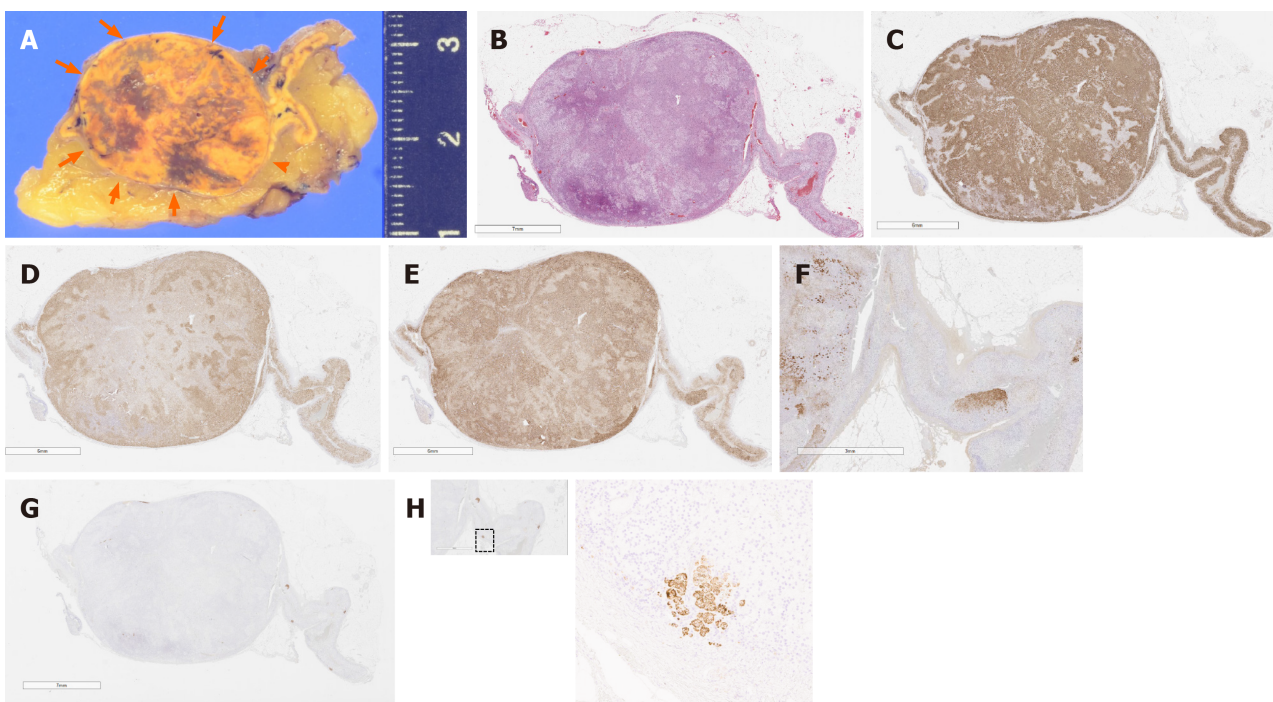


Figure 4 Pathological findings regarding the adrenocortical adenoma and attached adrenal cortex. A: Cut surface of the tumor and multiple small nodules. The resected tumor (arrows), measuring 2.5 cm × 2.3 cm × 2.0 cm in size, had a heterogeneous yellow and brown appearance. In addition, small cortical nodules less than 3 mm in diameter are also seen; B: Loupe. Upon hematoxylin and eosin staining, the tumor was histopathologically diagnosed as adrenocortical adenoma; C: Loupe. The adrenocortical adenoma was immunohistochemically positive for HSD3B2; D: Loupe. The adrenocortical adenoma was immunohistochemically positive for CYP17A; E: Loupe. The adrenocortical adenoma was immunohistochemically positive for CYP11B1; F: × 10. In the attached adrenal cortex, DHEA-ST expression was reduced, but not by the same extent as that in full-blown Cushing's syndrome; G: Loupe. CYP11B2 expression was completely negative in the adenoma; H: × 100. In the attached adrenal cortex, there were several aldosterone-producing cell clusters with positive CYP11B2 in the zona glomerulosa.

admixed with yellow and brown areas. The tumor was histologically diagnosed as adrenocortical adenoma according to the criteria of Weiss^[11] (Figure 4B). Subsequent immunohistochemical examination revealed that the tumor cells were positive for HSD3B2, CYP17A, and CYP11B1 (Figure 4C-E), consistent with the finding of cortisol-producing adrenocortical adenoma. The zona reticularis of the adjacent adrenal cortex was atrophic, with decreased DHEA-ST immunoreactivity (Figure 4F). CYP11B2 immunoreactivity was completely absent in this adenoma (Figure 4G), but in the adjacent non-neoplastic adrenal tissue, multiple CYP11B2-positive adrenocortical micronodules or cell clusters were detected at the subcapsular area, consistent with the histological finding of “Multiple adrenocortical micronodules” (Figure 4H). Therefore, these aldosterone-producing adrenocortical micronodules or cell clusters were

histopathologically diagnosed as the responsible lesion of PA in this patient.

The clinical control of his hypertension was achieved with two antihypertensive drugs, including amlodipine (5 mg) and eplerenone (50 mg). The hormonal examinations indicated the following: PAC, 374 pg/mL; renin activity, 3.5; ARR, 107; and cortisol, 12.4 µg/dL.

DISCUSSION

We report a case with concomitant bilateral PA and cortisol-producing right adrenocortical adenoma resulting in SCS. The inferences drawn from the present case are as follows: (1) PA and SCS can coexist in AI, and it is important to determine whether those two endocrinopathies could be due to a tumor; and (2) The detailed pathological evaluation revealed different sources of aldosterone and cortisol excess: the former in micronodules or clusters and the latter in an adenoma, which should highlight the importance of careful examination of the resected adrenal gland in this particular case.

The frequency of the concomitant presence of SCS and PA has been reported to be in the range of 11.3%-53.8%^[7-10], which may depend upon various factors pertaining to the studied population^[12], degree of hypertension^[13], or institutions at which the evaluation was conducted^[7,14]. Some clinical patient characteristics have been reported in the cases harboring SCS and PA concomitantly^[7,10,15], whereas the presence of diabetes mellitus (DM) may be more prevalent in PA patients with SCS compared with those without SCS. Cortisol rather than aldosterone has been considered to influence the onset or development of DM, although the presence of DM was not noted in our case. In addition, Furuta *et al*^[10] reported that the average size was larger in PA patients with SCS (3.0 cm) than in PA patients without SCS (1.5 cm), and the maximum size of the adenoma was 2.5 cm in our case. The presence of DM and/or the larger adenoma sizes quantified with imaging could provide important information regarding the coexistence of PA and SCS, but endocrinological confirmation should be required. The degree and/or duration of increased production of cortisol may contribute to the presence of the clinical characteristics of SCS.

The clinical diagnosis of SCS has been considered difficult in some cases because of the rather stringent clinical criteria of SCS. In this case, the results of normal cortisol concentrations in the early morning, dexamethasone suppression tests (1 mg and 8 mg), suppression of ACTH in the early morning, and findings of adrenal scintigraphy with increased uptake in the diseased side and decreased uptake in the normal side met the SCS criteria. However, it is also true that the cortisol concentration at midnight was relatively low, indicating that the preservation of the diurnal variation of cortisol and the normal response of ACTH in the CRH challenge test did not meet the criteria of SCS. In addition, the supplementation of steroid therapy after adrenalectomy, which constitutes one of the SCS criteria, was not necessarily required in this case. These findings may be attributed to the degree of production of cortisol in the adenoma and the preserved cortisol-producing function in the ipsilateral non-neoplastic adrenal tissue and the adrenal gland on the contralateral side. However, the pathological findings in this case did provide important information regarding the inconsistent clinical findings above, including the ability of the adenoma to produce cortisol and the status of the adjacent non-neoplastic adrenal tissue.

In patients with SCS and PA, careful interpretation of the results of AVS is generally required because the aldosterone/cortisol ratio is reduced on the diseased side and elevated on the normal side. In our present case, the lateralized ratio was increased in the left adrenal gland before the ACTH infusion, although the difference was not marked after the ACTH infusion. These findings are also considered to be attributed to the increased ability of the adenoma to produce cortisol and to the preserved function of the adrenal gland. The localized diagnosis of PA should be carefully interpreted in patients with a coexistence of PA and SCS.

Clinical evaluations regarding the PA in the present case include the following: negative captopril challenge test, positive saline loading test, and bilateral PA on AVS. These findings indicated the potential presence of idiopathic hyperaldosteronism (IHA), which is frequent among cases of PA^[16]. However, detailed pathological examinations did reveal that the micronodular hyperplasia detected suggested the bilateral micronodular hyperplasia as a responsive lesion of PA in this case. These detailed pathological examinations, especially the immunohistochemical analysis of steroidogenic enzymes involved in cortisol and aldosterone biosynthesis in the resected adrenal tissue, did provide pivotal information regarding the definitive

diagnosis of the adrenocortical lesions producing excessive amounts of two different adrenocortical hormones.

CONCLUSION

We reported a case of hypertension and right AI with concomitant SCS and bilateral PA based on clinical evaluations. Detailed pathological examination of the resected adrenal tissue did reveal that the patient had a cortisol-producing adrenocortical adenoma and micronodular hyperplasia in the nonneoplastic adrenal tissue or that cortisol and aldosterone were produced in the different adrenocortical lesions. It is important to assess causative diseases carefully in those harboring concomitant PA and SCS in patients with AI.

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