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Case Report

Aldosterone- and Cortisol Co-secreting Adrenal Cortical Neoplasm With Lipomatous and Myelolipomatous Metaplasia

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Abstract

We report a case of a 58-year-old woman with a history of hypertension diagnosed at aged 35 years, on 5 antihypertensive agents and a history of intermittent spontaneous hypokalemia, was found to have a 6-cm left adrenal mass on computed tomography scan of the abdomen. The unenhanced computed tomography attenuation of the adrenal mass was −16 Hounsfield units (HU). The biochemical evaluation showed potassium of 2.8 mEq/L (SI unit, mmol/L) (reference range, 3.5-5.0), plasma aldosterone concentration of 61.3 ng/dL (SI unit, 1701 pmol/L) with plasma renin activity of 0.4 ng/mL/h (SI unit, μg/L/h). An overnight 1-mg dexamethasone suppression test showed nonsuppressible serum cortisol of 10.8 μg/dL (SI unit, 298 nmol/L). Dehydroepiandrosterone sulfate and ACTH were measured at 24.5 μg/dL (age-adjusted, 26-200) (SI unit, 0.66 μmol/L; 0.70-5.43) and <5 pg/mL (SI unit, < 1.1 pmol/L), respectively. Left adrenalectomy was performed and hydrocortisone therapy was initiated. Postoperatively and thereafter, her blood pressure was controlled with no antihypertensive agent. Seven months later, hydrocortisone therapy was stopped once her cortisol level had normalized. Pathology showed adrenal cortical neoplasm of uncertain malignant potential with associated lipomatous and myelolipomatous metaplasia. This is a rare case of aldosterone and cortisol co-secreting adrenal cortical neoplasm of uncertain malignant potential with lipomatous and myelolipomatous metaplasia. Although the majority of cases of myelolipoma are benign and nonfunctioning, this case emphasizes the importance of thorough hormonal and morphologic evaluation of the tumor.

Key Words: adrenal cortical neoplasm, primary aldosteronism, Cushing syndrome

Abbreviations: CT, computed tomography; HU, Hounsfield unit; MRI, magnetic resonance image; PAC, plasma aldosterone concentration.

Adrenal lipomatous tumors are uncommon fatty tumors of the adrenal glands with myelolipoma being the most common histologic feature [1]. Adrenal myelolipoma is a benign adrenal cortical neoplasm composed of fat and myeloid tissue, commonly diagnosed if fat composition of tumor is more than 50% on cross-sectional imaging studies. The myelolipomatous metaplasia is a secondary degenerative change in primary adrenal tumor, usually seen in benign adrenocortical adenomas and rarely in adrenocortical carcinomas and cortical neoplasms of uncertain malignant potential [2]. Adrenocortical neoplasms are classified as benign or malignant based on modified Weiss score; when the criteria are not clear, the tumor is classified as a neoplasm of uncertain malignant potential. Because adrenal lipomatous tumors are usually benign and nonfunctional, patients with these tumors often do not undergo hormonal evaluation. In this report, we present a case of aldosterone and cortisol co-secreting adrenal cortical neoplasm of uncertain malignant potential with lipomatous and myelolipomatous metaplasia.

Case Presentation

A 58-year-old woman with a history of hypertension and intermittent hypokalemia presented for left flank pain. A noncontrast computed tomography (CT) scan was performed, showing a left ureteropelvic junction stone, left kidney stone, and an incidental apparent myelolipoma measuring 6.0 × 4.7 × 4.2 cm with an unenhanced CT attenuation of −16 Hounsfield units (HU) (Fig. 1A). She was referred to a urologist who performed lithotripsy. Twenty months later, a repeat noncontrast abdominal CT scan showed a stable left adrenal mass measuring about 5.3 cm in size and a normal-appearing right adrenal gland without radiologic evidence of nodularity or hyperplasia (data not shown). A further characterization by magnetic resonance imaging (MRI) studies showed a left adrenal mass measuring 5.4 × 5.2 cm with a heterogenous macroscopic fat distribution consistent with the diagnosis of myelolipoma (Fig. 1B and C). Eventually, she was referred to the endocrinology for further evaluation.

The patient was diagnosed with hypertension at age 35 years. Over the course of years, 5 different antihypertensive medications including amlodipine 2.5 mg daily, hydrochlorothiazide 25 mg daily, losartan 100 mg daily, metoprolol 200 mg daily, and spironolactone 100 mg daily have been gradually introduced to control hypertension. Review of the records demonstrated intermittent spontaneous hypokalemia ranging from 3.0 to 3.2 (SI unit, 3.5–5.0 mmol/L) years before initiation of spironolactone.

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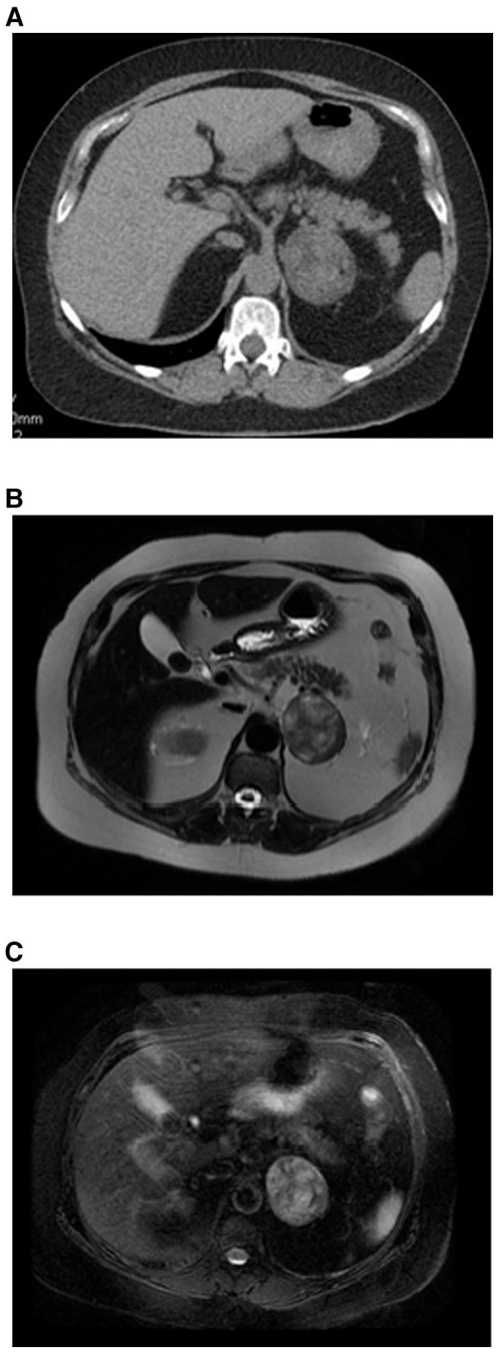

Figure 1. A computed tomography image of the abdomen without contrast demonstrating a well-circumscribed but heterogenous ~6-cm axial left adrenal mass (A). An axial T1-weighted magnetic resonance image revealed a 5.4 × 5.2 cm left adrenal mass that was largely hyperintense with a lower intensity periphery (B). On an axial T2-weighted magnetic resonance imaging, the mass has a heterogeneous signal intensity with the majority of hyperintensity areas (C).

The patient reported a history of easy bruising for about 5 years with a recent worsening of 1-year duration, but did not report weight gain, proximal muscle weakness, striae, fragility fractures, height loss, or other symptoms of hypercortisolism. On physical examination, the patient's blood pressure was measured at 115/63 mm Hg, pulse at 70/min, height at 157.5 cm, with weight of 80.7 kg and body mass index of 32.6 kg/m^2. The remainder of the physical examination was unremarkable without stigmata of Cushing syndrome.

Diagnostic Assessment

Results of biochemical evaluation are shown in Table 1. In brief, initial results at urology and repeated results after withholding spironolactone for 4 weeks as recommended by the recent guidelines [3] revealed marked elevated plasma aldosterone concentration (PAC) of 65.9 and 61.3 ng/dL (SI unit, 1828 and 1701 pmol/L) with suppressed plasma renin activity of 0.1 and 0.4 ng/mL/h (SI unit, μg/L/h), respectively, and unsuppressed morning serum cortisol levels following an overnight 1-mg dexamethasone of 13.1 and 10.8 μg/dL (SI unit, 361 and 298 nmol/L), respectively. Plasma fractionated free metanephrines and plasma dehydroepiandrosterone sulfate were normal. A 24-hour urine free cortisol was elevated with suppressed plasma ACTH. Taken together, these results supported primary aldosteronism and adrenal Cushing syndrome.

Confirmatory tests for primary hyperaldosteronism were not pursued given spontaneous intermittent hypokalemia and PAC > 20 ng/dL (SI unit, > 554 pmol/L) according to the 2016 Endocrine Society Clinical Practice Guideline on the Management of Primary Aldosteronism [3]. Adrenal venous sampling for lateralization was not performed because concomitant hypercortisolism may cause misinterpretation of cortisol-corrected aldosterone [4]. Given completely normal-appearing right adrenal gland and a large size of left adrenal mass, it was deemed that the left adrenal mass was an aldosterone- and cortisol-co-secreting tumor. The patient was referred to the urologist for left adrenalectomy.

Treatment

The patient underwent a robot-assisted left adrenalectomy. On postoperative day 1, expectedly, the patient began experiencing nausea and postural dizziness and her systolic blood pressure was low 100 at mm Hg. Postoperative laboratory data showed normal PAC of 6.2 ng/dL (SI unit, 172 pmol/L) and a low cortisol level of 2.3 μg/dL (SI unit, 63.4 mmol/L) (Table 1) with normal potassium levels. A stress dose hydrocortisone regimen was initiated for adrenal insufficiency, and her symptoms gradually improved over 48 hours.

Outcomes and Follow-up

The patient was discharged on a replacement regimen of hydrocortisone and was seen at the outpatient clinic 4 weeks after the left adrenalectomy. Her blood pressure was 100/72 mm Hg without any antihypertensives but she was on hydrocortisone 15 mg in the morning and 10 mg in the afternoon. Seven months later, her morning cortisol measured without hydrocortisone for ~24 hours returned normal 10.2 μg/dL (SI unit, 281 nmol/L). Hydrocortisone therapy was stopped. Her blood pressure was 100/70 mm Hg and serum potassium remained normal, ranging from 4.3 to 4.5 mEq/L (SI unit, mmol/L) without antihypertensives and potassium supplement. The patient lost 18.1 kg of weight and then had a body mass index of 25.2 kg/m^2 since her left adrenalectomy. Her hemoglobin A1c level improved from 6.5% (SI unit, 48 mmol/mol) before her adrenalectomy to 6.2% (SI unit, 44 mmol/mol) in 4 months and 5.6% in 11 months (SI unit, 38 mmol/mol) after surgery. Dual-energy X-ray absorptiometry (GE Lunar Prodigy Advance) showed normal her bone mineral density at the lumbar spine and left and right femoral necks of 1.304, 1.008, and 0.999 g/cm^2 with a T-score of 1.0, −0.2, and −0.3, respectively,

Table 1. Laboratory data

Test (reference range)	Initial evaluation at the urology office, 1 wk after withdrawing spironolactone and HCTZ	Four weeks after withdrawing spironolactone and HCTZ with potassium supplement	One day after left adrenalectomy
Serum potassium (mEq/L, 3.5-5.1) (SI unit, mmol/L)	2.8	3.7	3.8
PAC (ng/dL) (SI unit, pmol/L)	65.9 (SI unit, 1828)	61.3 (SI unit, 1701)	6.2 (SI unit, 172)
PRA (ng/mL/h) (SI unit, μg/L/h)	0.1	0.4	4.2
Plasma DHEA-S (μg/dL, 26-200) (SI unit, μmol/L, 0.70-5.43)	24.5 (SI unit, 0.66)		
24-h urine free cortisol (μg/24-h, 4.0-50.0) (SI unit, nmol/24-h, 11-138)		70 (SI unit, 193.2)	
8 AM serum cortisol (μg/dL, 6.0-23.0) (SI unit, nmol/L, 165.5-634.6)		13.1 (SI unit, 361.4)	2.3 (SI unit, 63.5)
Serum ACTH (pg/mL) (SI unit, pmol/L)		<5 (SI unit, < 1.1)	
Plasma normetanephrine (0.00-0.89 nmol/L)	0.22		
Plasma metanephrine (0.00-0.49 nmol/L)	0.13		
Serum cortisol after an overnight 1-mg DST (μg/dL) (SI unit, nmol/L)	13.1 (SI unit, 361.4) (on a separate day from other tests)	10.8 (SI unit, 298.0) (on a separate day from other tests)	

Abbreviations: DHEA-S, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test; HCTZ, hydrochlorothiazide; PAC, plasma aldosterone concentration; PRA, plasma renin activity.

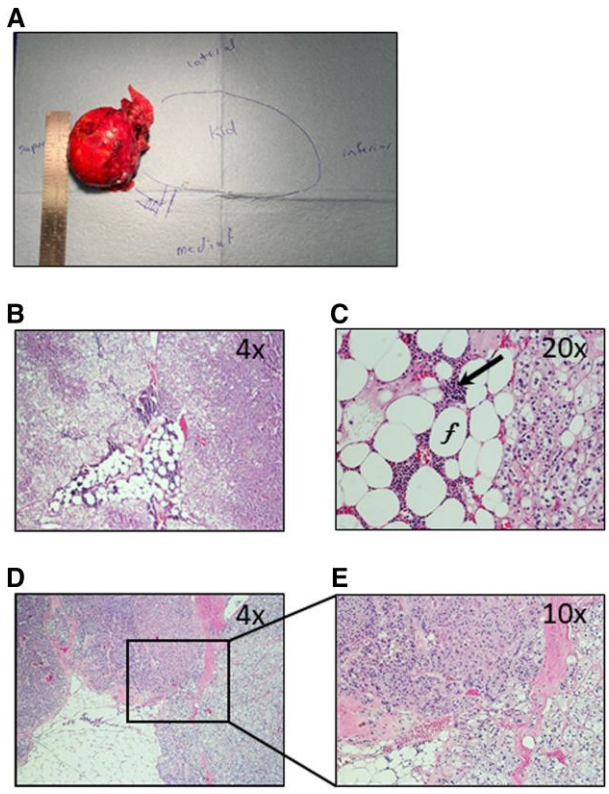

Figure 2. Pathology of the left adrenal mass. (A) Resected specimen of left adrenal mass. (B) Adrenal cortical neoplasm with myelolipomatous metaplastic foci scattered within the adrenal cortical neoplasm (×4, hematoxylin and eosin [H&E] stain). (C) The myelolipomatous metaplasia (left) showing fat (f) and myeloid (arrow), and clear cells (right) within the adrenal cortical neoplasm (×20, H&E stain). (D, E) Adrenal cortical neoplasm with lipomatous metaplastic foci (left upper) scattered within the adrenal cortical neoplasm (right lower) (D: ×4, H&E stain; E: ×10, H&E stain).

indicating that her mild hypercortisolism did not affect her skeleton significantly.

The tumor measured 7 × 5 × 4.2 cm and weighed 162 g (Fig. 2A). Histologic findings included <25% clear cells, lack of mitotic activity, scattered lipomatous, and myelolipomatous metaplastic foci without necrosis or capsular invasion. There was neither extraglandular extension nor lymphovascular invasion with the surgical margin free of tumor. The tumor was designated as having uncertain malignant potential because of the large size and areas that lack clear cells. Specifically, for myelolipomatous metaplasia, the fat within an adrenal cortical tumor was scattered (Fig. 2B–E).

Discussion

Adrenal myelolipoma is a benign adrenal cortex neoplasm composed of fat and myeloid tissue. On pathologic examination, myelolipoma is characterized by well-defined macroscopic fat, whereas myelolipomatous and lipomatous metaplasia has a scattered ill-defined foci of fat and myeloid tissue within a tumor [5]. Adrenocortical neoplasms are classified as benign or malignant based on modified Weiss score, when the criteria are not clear, the tumor is classified as a neoplasm of uncertain malignant lesion.

On a CT or MRI scan, myelolipomas can be diagnosed if the fat composition of a tumor is more than 50% [5]. On a noncontrast CT scan, myelolipoma has an attenuation of less than 0 HU, sometimes less than –50 HU. On a contrast CT scan, the hematopoietic tissue shows contrast enhancement. Fatty areas in myelolipoma have increased signal intensity on a T1-weighted MRI. On a T2-weighted MRI, fatty areas have increased signal intensity and bone marrow elements have moderately increased signal intensity [5] and there is a loss of signal on fat-saturated MRI. All these imaging characteristics were evident in the present case (Fig. 1).

Most myelolipomas are nonfunctional. Thus, myelolipoma is considered an exception for mandatory metabolic assessment of a newly discovered adrenal mass [6]. However, it was reported that endocrine dysfunction may exist in up to 7% of adrenal myelolipomas. In the current case, although imaging characteristics were consistent with myelolipoma, biochemical evaluation was pursued because the patient had resistant hypertension and spontaneous hypokalemia. Hypertension and hypokalemia can result directly from primary aldosteronism or from hypercortisolism leading to mineralocorticoid receptor activation by overwhelming the capacity of 11 beta-hydroxy steroid dehydrogenase type 2.

Initially, adrenal cortical tumors co-secreting cortisol and aldosterone were thought to be rare; however, now the prevalence of aldosterone and cortisol co-secretion is estimated at 5% to 21% of adrenal tumors. In patients with primary aldosteronism, evaluation for cortisol co-secretion is clinically important because it impacts diagnostic approaches such as adrenal venous sampling and postoperative management such as prevention of adrenal crisis after tumor removal. It is suggested that patients with primary aldosteronism and tumor size greater than 2.0 or 2.5 cm or diabetes mellitus need to be evaluated for hypercortisolism because the larger the tumor is, the more cortisol co-secretion exists [7]. Somatic mutations of the potassium channel *KCNJ5* gene were reported in 40% of aldosterone-producing adenomas. Yamada et al reported that some aldosterone and cortisol co-secreting tumors have same *KCNJ5* gene mutation, suggesting the origin to be aldosterone-producing adenomas [8].

Histopathological diagnosis of an adrenal tumor is challenging. The microscopic Weiss criteria is the best validated approach to differentiate between benign and malignant adrenal tumors. The 5 criteria used in updated Weiss system include (1) number of mitoses per 50 high-power field, (2) percentage of clear cells, (3) abnormal mitoses, (4) necrosis, and (5) capsular invasion [9]. A total score of ≥3 supports malignancy. In the current case, pathologic examination showed scattered lipomatous and myelolipomatous metaplastic foci without necrosis. This tumor is designated as having uncertain malignant potential because of the large size and areas that lack clear cells.

In summary, the adrenal tumor in the present case was consistent with the diagnosis of a benign apparent myelolipoma by imaging characteristics yet found not only to co-secrete aldosterone and cortisol, but also to be an adrenocortical neoplasm of uncertain malignant potential with lipomatous and myelolipomatous metaplasia.

Learning Points

- The importance of looking for symptoms, signs, and laboratory data point to adrenal hyperfunction in patients with adrenal myelolipoma, which is commonly considered nonfunctional.

- It is important to recognize aldosterone and cortisol co-secretion in adrenal tumors as related to different diagnostic approaches, perioperative management, and care of other comorbidities.

Contributors

All authors made individual contributions to authorship. S. J. and J. J. were involved in the diagnosis and management of this patient and manuscript submission. R. T. provided the histopathology section and preparation of histology images. F. P. was responsible for the patient's surgeries. All authors reviewed and approved the final draft.

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Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Original data generated and analyzed for this case report are included in the published article.

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