CASE REPORT

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Diagnosis and Management of Adrenocortical Carcinoma with Co-secretion of Cortisol and Aldosterone: A Case Report

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Abstract

Adrenocortical carcinoma (ACC) accounts for 0.05-2% of all malignant tumors. Forty-five percent of ACCs with secretory function have excess glucocorticoids alone and only less than 1% secrete aldosterone.

This is a case of a 44-year-old Filipino female with hypertension and a 12-year-history of an incidentaloma of the left adrenal gland, with recent-onset complaints of increasing abdominal girth, purple striae, amenorrhea, moon facies and a dorsocervical fat pad. Laboratory findings revealed low potassium levels, non-suppressed cortisol on dexamethasone test suggesting Cushing's syndrome and elevated aldosterone-renin ratio and plasma aldosterone concentration pointing to primary hyperaldosteronism. A computed tomography scan revealed a left-sided adrenal mass measuring approximately 23 cm in largest diameter suggestive of carcinoma without metastasis or lymph node involvement. Complete resection via open adrenalectomy was performed and histopathologic assessment revealed Adrenocortical Carcinoma with Weiss score of 4. The Ki-67 proliferative index was found to be >20%. Radiotherapy was done as an adjuvant treatment.

Although rare, co-secretion of cortisol and aldosterone can occur in functional tumors of adrenocortical carcinoma. Malignancy should always be considered in patients who present with a history of a unilateral adrenal mass and/ or in those with signs and symptoms of adrenal hormone excess. Thus, a proper assessment derived from a thorough medical history, physical examination and laboratory work-up is warranted in patients with an adrenal mass to ascertain the diagnosis and provide adequate management.

Key words: adrenocortical carcinoma, primary hyperaldosteronism, Cushing's syndrome, cortisol, aldosterone

INTRODUCTION

Adrenal cortical carcinoma (ACC), or adrenocortical carcinoma, is a rare condition with an annual incidence of approximately 1-2 per 1 million of the population and comprises 0.05-0.2% of all cancers.[1] It is highly malignant, often sporadic and linked to mutations in the tumor suppressor gene TP53, alterations in the Wnt/Beta-catenin pathway and overexpression of the insulin-like growth factor 2 (IGF2) cluster.[2] Patients with ACC may be asymptomatic and diagnosed incidentally only during imaging. However, 80% of these tumors are functional and may present with clinical features of adrenal hormone excess. Forty-five percent of these patients have an excess of glucocorticoids alone, 45% with glucocorticoids and androgens and approximately 10% with androgens alone.[3] An evaluation of the adrenal hormone status is warranted, followed by surgical resection of the tumor and adjuvant treatment with mitotane. Monitoring for recurrence is performed indefinitely, with an option for cytotoxic chemotherapy should there be progression or recurrence. This report presents a rare case of cortisol and aldosterone-secreting adrenocortical carcinoma with a clinical presentation of primary hyperaldosteronism and Cushing's syndrome, its diagnosis and management.

CASE

A 44-year-old Filipino female had complaints of increasing abdominal girth with reddish-purple striae on the abdomen and arms. The patient has no history of diabetes or asthma but is a known hypertensive of 6-year duration, with poor control despite 3 different anti-hypertensive maintenance medications. Her family history only revealed hypertension from both paternal and maternal sides, but no known history of malignancies. Twelve years prior, the patient also had a history of an incidental finding on a computed tomography (CT) scan of a left adrenal mass approximately 9 cm in largest diameter. She was advised work up during that time but was not able to comply and was lost to follow-up, thereafter. The patient's present complaint started 2 years prior to admission, wherein

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increasing abdominal girth was associated with gradually increasing abdominal pain, amenorrhea, build-up of a dorsocervical fat pad and a rounded appearance of the face. The condition was tolerated until the time of consult. The initial impression was that of Cushing's syndrome likely due to a functioning adrenal tumor. Laboratory tests taken include thyroid function tests, fasting blood glucose level, glycosylated hemoglobin, lipid profile, a complete blood count, electrolytes, liver and kidney function tests. The patient was found to have impaired fasting glucose and a subnormal potassium level. Correction of the serum potassium was done. An abdominal CT scan with contrast showed a large heterogeneously enhancing, well-circumscribed, noncalcified mass in the region of the left adrenal gland (Figures 1 and 2), measuring approximately 22.5 x 19.6 x 22.8 cm and with no other lesions found in the abdomen. The chest x-ray showed clear lung fields. Positron Emission Tomography (PET) scan did not reveal any evidence of metastasis in other sites of the body.

At this time, mineralocorticoid excess was considered due to the presentation of hypertension, hypokalemia and the presence of an adrenal mass. An overnight dexamethasone suppression test revealed a non-suppressed cortisol at 389.2 nmol/L (14.1 ug/dL) while plasma ACTH was low. These findings along with the clinical signs and symptoms suggested an excess of cortisol and pointed to ACTH-independent Cushing's syndrome. The dehydroepiandrosterone-sulfate (DHEA-S) and 24-hour urine metanephrine tests were within normal range ruling out androgen excess and pheochromocytoma, respectively. The computed aldosterone-renin ratio (ARR) of 33.475 ng/dl:ng/ml/hr indicated an excess of aldosterone. The patient's plasma aldosterone concentration was also increased at 47.20 ng/dL. In patients with a background of hypokalemic hypertension, strongly positive ARR and concurrently increased aldosterone levels, confirmatory testing for primary hyperaldosteronism (like saline infusion test) may not be necessary and can be deferred.[2]

The patient underwent unilateral adrenalectomy via open surgery with peri-operative steroid coverage which yielded a large, grey-tan, firm, ovoid mass that measured 260 x 235 x 155 mm and weighed 3800 grams (see Figure 3). On serial sectioning, the mass showed a predominantly solid, lobulated, yellow-tan cut surface with large hemorrhagic and necrotic areas occupying 40% of the mass. The microscopic examination revealed tumor invasion through the adrenal capsule, low grade with oncocytic features, presence of lympho-vascular invasion and negative margins. The histopathologic findings were consistent with adrenal cortical carcinoma. Post-operatively, chest and lung Positron Emission Tomography and Computed Tomography (PET-CT) scans did not detect metastasis or local recurrence. The patient's blood pressure decreased to normal level and there was no recurrence of hypokalemia. The Ki-67 index, however, had increased expression at >20% on immunostaining, hence, radiotherapy was subsequently done with advice for regular follow-up.

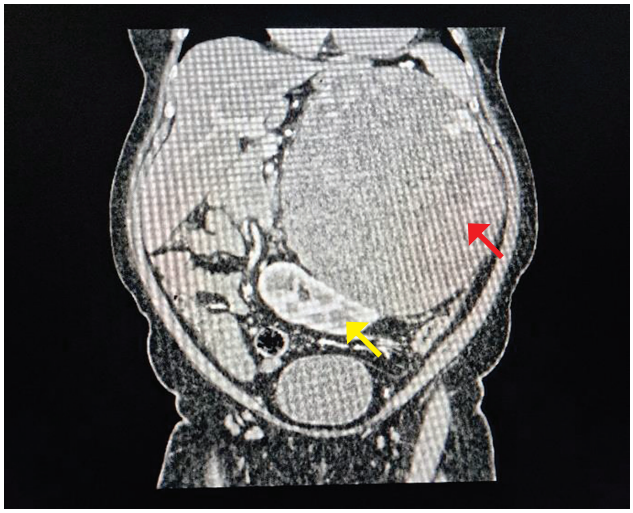

Figure 1. CT scan of the abdomen showing a large heterogeneously-enhancing mass *(red arrow)*, displacing the left kidney *(yellow arrow)* caudally and medially.

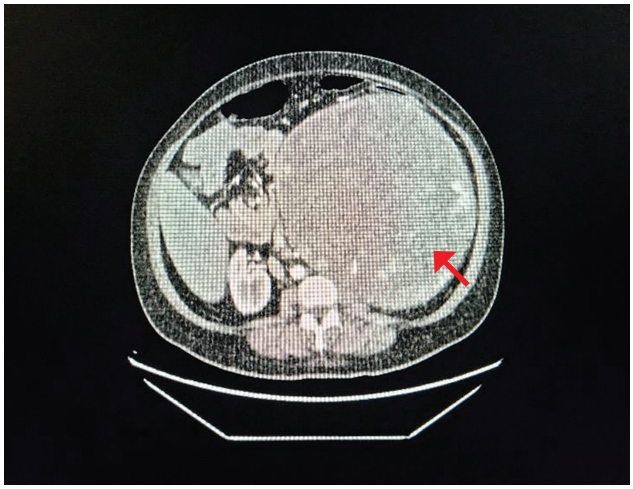

Figure 2. CT scan of the abdomen on axial view showing the left adrenal mass *(red arrow)* occupying the bulk of the left intraabdominal space.

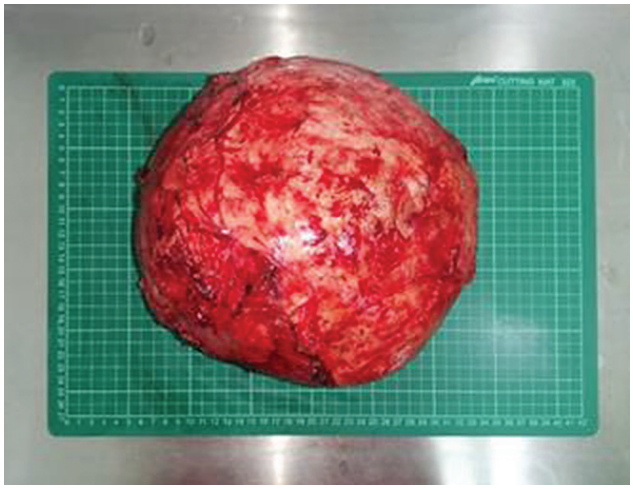

Figure 3. Adrenal mass obtained after surgery, measuring 260 x 235 x 155 mm.

DISCUSSION

ACC is an uncommon underlying cause of unilateral adrenal mass cases, with only an approximate prevalence of 2-5% and 0.05-2% of all malignant tumors.[1] It is a rare malignancy and has an annual incidence of 1 to 2 per million in the population. Women are more affected than men at a ratio of 2.5:1, with a mean age of onset between the 4th to 5th decades of life.[3] The diagnosis of malignancy relies on investigations of clinical, biological and imaging features before surgery and with the subsequent histopathological examination after surgery. Approximately 80% of ACC tumors are functional. Additionally, among the functional tumors, 45% may secrete glucocorticoids alone, 45% may secrete both glucocorticoids and androgens and 10% secrete androgens alone,[3] while only less than 1% of all tumors secrete aldosterone. Thus, the patients would usually present with features of hormone excess. For the case at hand, the patient presented with gradually increasing abdominal pain, increasing abdominal girth, purple striae, amenorrhea, moon facies and a buffalo hump, all of which are clinical manifestations of cortisol hypersecretion from Cushing's syndrome. Furthermore, the patient had a history of a unilateral adrenal mass, uncontrolled hypertension and hypokalemia. These features were suggestive of mineralocorticoid excess which warranted further work-up. As ACC tumors often have an overproduction of glucocorticoids alone or of both glucocorticoids and androgens, the patient's presentation of both glucocorticoid and mineralocorticoid excess was uncommon.

The risk for ACC in a unilateral adrenal mass increases with tumor size, with the index of suspicion increasing for tumors more than 4-6 cm.[3] Adrenal malignancy was suggested by the heterogeneous enhancement and large size of the mass (approximately 23 cm in its largest diameter) with the presence of neovascularization on imaging. Assessment for metastasis was imperative in the patient. Metastasis in ACC most frequently occurs in the liver and lung.[2] Evaluation of the lungs by a chest x-ray is the initial imaging modality used in the detection of pulmonary metastasis. A CT scan of the whole abdomen with contrast media is informative and provides adequate sensitivity for the assessment of the adrenal mass and the detection of hepatic metastasis.[4] Additionally, a PET-CT scan would also provide information on possible metastasis on other sites of the body which may influence therapeutic decision-making.[3] With the imaging procedures done on the patient, other than the visualized adrenal mass, there were no other lesions, lymphadenopathies, or evidence of metastasis found.

Patients with an adrenal mass are worked up for hormone excess. Plasma metanephrine or 24-hour urine metanephrine is measured to assess for catecholamine excess that may indicate the presence of pheochromocytoma.[2] In this patient, plasma metanephrine (normal range <0.5 nmol/L)[3] and 24-hour urine metanephrine (normal range 24-96 mcg/day but may vary in other centers)[3] were within the normal range. In the workup for cortisol excess, screening or confirmatory testing include the following: increased 24-hour urinary free cortisol excretion, failure to suppress morning cortisol level after exposure to dexamethasone overnight and evidence of loss of diurnal cortisol secretion along with high levels at midnight[5] – which is the time at which cortisol secretion is physiologically at its lowest.[3] When results are equivocal, further confirmation may be done by performing a low-dose dexamethasone suppression test.[5] An overnight dexamethasone suppression test was done for the patient in which 1 mg of dexamethasone was given at 11 PM and cortisol level was determined at 8 AM the subsequent day. The patient's cortisol level was found to be elevated and unsuppressed at 389.2 nmol/L which is greater than the cutoff of 50 nmol/L. Plasma ACTH taken was suppressed at 1.04 pg/mL. Low levels of ACTH (<5 pg/mL) would support cortisol excess that is not dependent on ACTH.[2]

In the work-up for mineralocorticoid excess, the clinical suspicion of such is made in the presence of hypertension and at least one risk factor.[2] These risk factors include the presence of an adrenal mass, drug-resistant or severe hypertension needing >3 antihypertensive medications, hypokalemia and family history of early-onset hypertension or cerebrovascular events at <40 years of age. The patient was clinically suspected of mineralocorticoid excess due to poorly controlled hypertension, persistent hypokalemia and the presence of an adrenal mass. Screening is done by measuring aldosterone and renin levels and subsequently assessing the aldosterone-renin ratio. The aldosterone-renin ratio (ARR) is "positive" for mineralocorticoid excess if the ratio is >30 ng/dL per ng/mL/hr with a concurrently high normal or increased aldosterone level.[6] The patient's ARR was noted to be elevated at 33.475 ng/dL:ng/mL/hr and plasma aldosterone concentration was high at 47.20 ng/dL. Normal levels of plasma aldosterone concentration range from 7 to 30 ng/dL.[6] The second step in the assessment for mineralocorticoid excess is to do confirmatory testing to show that the excess in aldosterone is produced autonomously or independently of the renin-angiotensin system. However, confirmatory testing may be omitted when any of the following factors are present: elevation of the plasma aldosterone concentration >20 ng/dL, presence of hypokalemia and/or undetectable plasma renin activity.[6] The patient presented with hypokalemic hypertension and had a plasma aldosterone concentration of 47.20 ng/dL, thus, confirmatory testing was deferred. Patients with primary hyperaldosteronism generally should undergo adrenal vein sampling (AVS) to distinguish between unilateral or bilateral aldosterone excess.[3] This, however, may not be done in patients suspected of having an adrenocortical carcinoma.[7]

Evaluation of overproduction of adrenal androgen precursors should also be done in the context of an adrenal mass with the potential of androgen excess or potential adrenocortical cancer. Elevation of dehydroepiandrosterone-sulfate (DHEAS) may be frequently seen in the context of

ACC.[2] Hence, DHEAS levels were taken and were within normal range in this patient. Reference ranges for DHEAS differ based on age and sex, but a 44-year-old female generally has normal DHEAS levels between 57.3 and 279.2 mcg/dL.[8]

Staging in ACC is mandatory to assess for prognosis and treatment options. The TNM staging system is recommended and defines Stage I and Stage II as strictly localized tumors that differ in size at ≤5 or >5 cm, respectively. Stage III ACC is characterized by infiltration of the surrounding tissue, the presence of positive regional lymph nodes, or a tumor thrombus in the vena cava and/ or renal vein, whereas Stage IV ACC differs from the rest by the presence of distant metastasis. Stages I-III are considered localized ACC and complete resection by surgery is the treatment of choice.[4] As the patient's mass was well-circumscribed and did not have evidence of regional lymph node involvement, infiltration of the surrounding tissue, or distant metastasis on imaging procedures, the case was assessed to be that of Stage II. Open surgery is the standard surgical approach for patients with confirmed or highly suspected ACC.[9] Complete resection of the adrenal tumor by open adrenalectomy was, therefore, performed.

Following surgery, pathological assessment of the specimen was performed to verify the diagnosis, evaluate prognostic markers and assess the need for adjuvant therapy.[10] Macroscopically, ACC tumors are large and heterogeneous, with a surface that ranges from brown to orange or yellow, depending on the lipid content of their cells. Necrosis is almost always present. Gross examination of the specimen revealed a large, slightly firm, ovoid mass measuring 26.0 x 23.5 x 15.5 cm and weighing 3.8 kilograms. It presented with a smooth, glistening, grey-tan external surface, and serial sectioning revealed a predominantly solid cut surface with hemorrhagic and necrotic areas occupying approximately 40% of the entire mass. On microscopic examination, the evaluation of the specimen makes use of the Weiss score, which is the best-validated score for establishing ACC. It takes into account the presence of necrosis, invasion of various structures, diffuse architecture, atypical mitosis and the nuclear grade. A score of ≥3 defines ACC, while a score of 1-2 supports adrenal adenoma.[4] The presence of necrosis, atypical mitotic figures, capsular invasion and lympho-vascular invasion in the patient's evaluated specimen, favor the diagnosis of carcinoma with a Weiss score of 4. Immunohistochemical staining for the Ki-67 proliferation index helps to define the prognosis of ACC. A Ki-67 <10% is indicative of slow to moderate growth velocity, whereas a Ki-67 of ≥10% is associated with poor prognosis and a high risk of recurrence and rapid progression.[1] The immunohistochemical staining revealed a Ki-67 of >20% in the patient. Due to the high risk of recurrence, patients with a high proliferation index are offered adjuvant therapy with mitotane and/ or radiotherapy.[4] After an individualized discussion with the patient and taking into account her risk factors and potential adverse effects, a decision was made to perform radiotherapy. Although there is ongoing debate regarding the subset of patients that are recommended radiotherapy, evidence suggests a potential benefit of this treatment in all stages of ACC, and it is more commonly recommended for patients with a high risk of recurrence or those with Stage 3 disease.[10]

CONCLUSION

A thorough history and physical examination along with a comprehensive laboratory work-up is warranted in patients with an adrenal mass to ascertain the diagnosis and provide adequate management. Although rare, adrenocortical carcinoma can be the primary cause of an adrenal mass, and although largely uncommon, it can cause hypersecretion of both aldosterone and cortisol that would, therefore, present with clinical features associated with the excess of these hormones. Uncontrolled hypertension and hypokalemia are often indicators of primary hyperaldosteronism on a background of an adrenal mass. On the other hand, the clinical manifestations of Cushing's syndrome would highlight an excess of cortisol. These include, but are not limited to, the presence of a buffalo hump or the formation of a dorsocervical fat pad, moon facies, abdominal striae and weight gain. The presence of an adrenal mass most often points to an adrenal adenoma; however, certain features favor the presence of an adrenal carcinoma. These features include the large size of the adrenal mass greater than 4-6 cm in diameter, the heterogeneous character of the mass on imaging especially at >20 HU and invasion to surrounding structures. The presentation of some or all of these features should, therefore, highlight primary adrenal malignancy as a possible cause. Complete surgical resection is the standard of care in patients with adrenocortical carcinoma. Determination of the Ki-67 proliferation index is a prognostic marker that would then guide post-operative treatment. Adjuvant therapy with mitotane and/ or radiotherapy is done, taking into account the patient's risk factors and prognostic markers, balanced with the likely adverse effects of treatment. Regardless of the prognosis and treatment, lifelong monitoring for recurrence is recommended.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
MMA: Conceptualization, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration; **LMTG:** Conceptualization, Investigation, Writing – original draft preparation, Writing – review and editing

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