Use of Steroidogenic Precursors for Evaluation of Adrenocortical Carcinoma in Adrenal Masses: A Case Series

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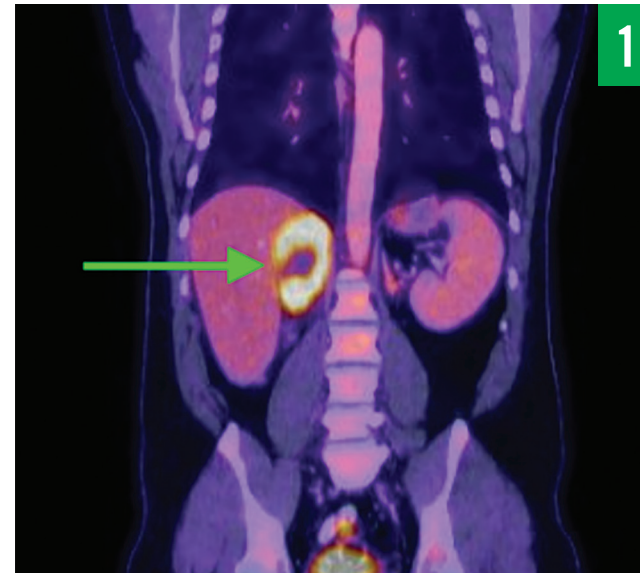
The prevalence of incidentally discovered adrenal masses continues to rise as the use of cross-sectional imaging increases.[1] Most of these masses are benign, consisting of nonfunctioning adenomas (80%), mild cortisol-producing adenomas leading to subclinical Cushing syndrome (5%), pheochromocytomas (5%), and aldosterone-secreting adenomas (1%). However, 2.5% of adrenal masses represent metastatic disease, and 5% are adrenocortical carcinoma (ACC).[2,3] Given the poor prognosis of ACC, early diagnosis and curative resection are critical.[2-4] Since most ACC cases are functional, the use of adrenal steroid precursor hormones such as 17-hydroxyprogesterone (17-OHP), androstenedione, 11-deoxycortisol, and 11-deoxycorticosterone can help expedite time to diagnosis.[2,3]

CASE REPORTS

Hormonal evaluations of all 3 of the following patient's cases are summarized in the **Table**.

Patient 1. A 40-year-old man presented with right upper quadrant abdominal pain. Computed tomography (CT) scans revealed a 7-cm heterogenous right adrenal mass with areas of necrosis and periaortic and portacaval lymphadenopathy, a finding not noted on CT scans performed 2 years earlier. On further history, the patient reported having night sweats, a 6.8-kg weight loss, and decreased appetite. Positron emission tomography (PET)/CT scans demonstrated a hypermetabolic 5.6×4.4-cm right adrenal mass with central necrosis and adjacent lymph nodes (**Figure 1**). The patient underwent right adrenalectomy, with pathology test results confirming poorly differentiated partially necrotic ACC, with 2 paraaortic lymph nodes negative for metastatic disease.



PET/CT image of patient 1, with the arrow pointing to a hypermetabolic 5.6x4.4-cm right adrenal mass with central necrosis.

Patient 2. A 76-year-old woman presented with unexplained 13.6-kg weight loss. She denied any sick contacts or travel history, and age-appropriate cancer screenings were up to date and negative. CT scans revealed a well-circumscribed 3.4-cm right adrenal mass with elevated Hounsfield units (HU) of 70 and low absolute contrast washout of 34%. Laboratory workup revealed mildly elevated levels of plasma and urine normetanephrines, which were thought to be secondary to serotonin-norepinephrine

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Table. Hormonal Evaluations of 3 Patients

Analyte	Patient 1	Patient 2	Patient 3	Reference Range
Aldosterone, ng/dL	<4.0	<4.0	Not tested	<21
Renin, ng/mL/h	0.6	<0.6	Not tested	Sodium replete, 0.6-3.0
8 AM cortisol (following 1 mg dexamethasone suppression), µg/dL	<1.0	1.7	Not tested	<1.8
24-h urine free cortisol, µg/24 h	Not tested	Not tested	97	6-42
11-deoxycorticosterone, ng/dL	Not tested	26	Not tested	<10
11-deoxycortisol, ng/dL	370	Not tested	320	10-79
Plasma free normetanephrine, nmol/L	0.51	1.20	0.52	<0.90
Plasma free metanephrine, nmol/L	0.20	<0.20	<0.20	<0.50
Urinary normetanephrine, µg	168 (119-451 µg/24 h)	564 (82-500 µg/24 h)	Not tested	Varies by case
Urinary metanephrine, µg	64 (44-261 µg/24 h)	51 (45-290 µg/24 h)	Not tested	Varies by case
Dehydroepiandrosterone sulfate, µg/dL	546 (57-522 µg/dL)	72 (5.3-124 µg/dL)	<0.5 (9.7-159 µg/dL)	Varies by case

reuptake inhibitor use. Hyporeninemic hypoaldosteronism was also noted and prompted further investigation of the 11-deoxycorticosterone level, which was elevated (**Table**). PET/CT scans showed a heterogenous, hypermetabolic right adrenal mass now measuring 4.7 cm (**Figure 2**). The patient underwent laparoscopic right adrenalectomy, with pathology test results confirming oncocytic ACC with focal capsular invasion.

Patient 3. A 70-year-old woman presented with nausea, dizziness, and a thoracic vertebral fracture requiring kyphoplasty. Five years prior, she had presented to another facility with symptoms of Cushing syndrome, a 5-fold elevation in 24-hour urine free cortisol, and a 10-cm left adrenal mass. She had undergone left adrenalectomy, with pathology test results noting ACC with extensive necrosis and focal invasion into surrounding tissue with local vascular invasion. She had completed radiotherapy to the left adrenal bed and had begun therapy with mitotane, hydrocortisone, and fludrocortisone. PET/CT scans performed 2 years later noted a 7-mm hypermetabolic right lung nodule without focal adrenal uptake.

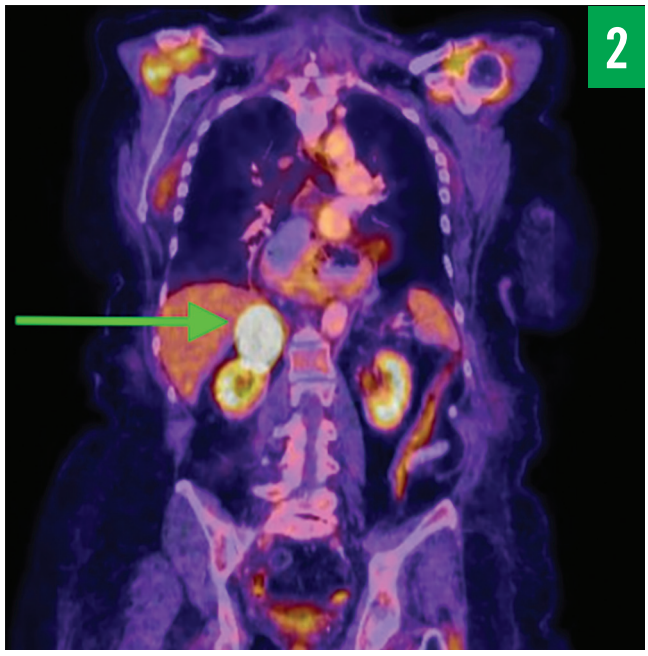
After 2 additional years, the patient presented for a second opinion, with workup revealing elevated 11-deoxycortisol levels, a stable right lung nodule, and a hypermetabolic 4.2 × 3.2-cm left adrenal bed mass with focal uptake in the left hepatic lobe on PET/CT, likely representing recurrent ACC (**Figure 3**). Given the malignancy recurrence while on mitotane, the medication was discontinued. The patient then underwent extensive surgical resection with left partial hepatectomy, splenectomy, distal pancreatectomy, partial gastrectomy, partial left hemidiaphragm resection, resection of the left retroperitoneal adrenal bed mass, and left radical nephrectomy.

DISCUSSION

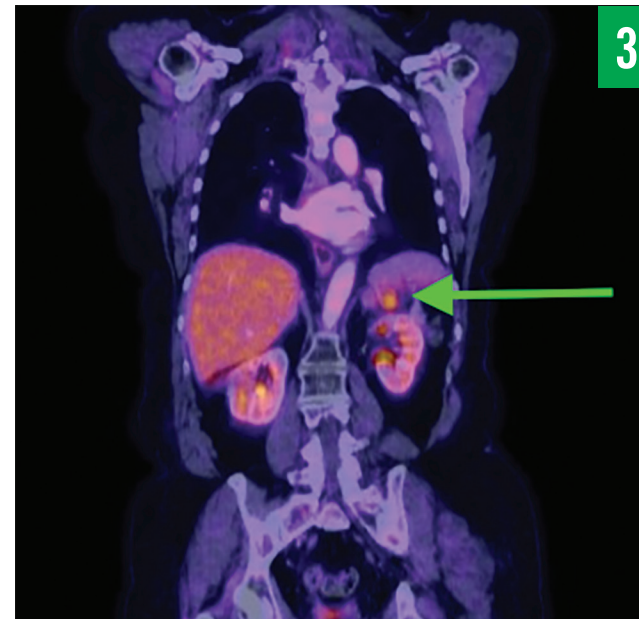
While ACC occasionally develops as part of hereditary syndromes, most adult-onset cases are sporadic, accounting for approximately 1 to 2 cases per million per year.[2,3] The prognosis of ACC is poor, with a median survival rate of 3 to 4 years.[2,5] However, 5-year survival increases to 60% to 80% for tumors confined to the adrenal gland, since complete surgical resection is the only curative treatment.[2,6] Since 5-year survival decreases to 0% to 28% in metastatic disease, early detection and diagnosis is imperative.[2]

In the 3 cases discussed here, hormone evaluation was notable for elevated 11-deoxycortisol levels in 2 patients and an elevated 11-deoxycorticosterone level in the third patient. Approximately two-thirds of ACC cases are hormonally active,[3,5-7] While hypercortisolism is estimated to be present in 50% to 80% of functional ACCs, defects in steroid biosynthesis enzymes can also lead to inefficient end hormone production and buildup of steroid precursors.[5,6] Clinical features of ACC can include rapid development of hypercortisolism symptoms including hypokalemia or muscle weakness, androgen excess such as hirsutism or virilization in women, or estrogen excess leading to gynecomastia in men or postmenopausal bleeding in women.[2,3,8,9] Hypokalemia with hypertension is commonly observed and is usually due to overproduction of mineralocorticoid precursors such as 11-deoxycorticosterone or activation of mineralocorticoid receptors through 11β-hydroxysteroid dehydrogenase by excess cortisol.[6] Less than 1% of all ACCs produce aldosterone.

Certain hormone patterns, such as cortisol overproduction or co-secretion of cortisol and androgens, can raise suspicion for functional ACCs.[5] Likewise, although rare, the presence of



PET/CT image of patient 2, with the arrow pointing to a hypermetabolic 4.7-cm right adrenal mass.



PET/CT image of patient 3, with the arrow pointing to a hypermetabolic 4.5×3.2 cm lobulated soft tissue mass in the posterior left upper quadrant, within the left adrenalectomy bed.

estrogen secretion in men or postmenopausal women is highly suggestive of ACC.[9] Steroidogenic precursors, such as 17-OHP, 11-deoxycortisol and 11-deoxycorticosterone are not part of the standard adrenal mass workup but can be useful in evaluating for ACC when suspicion is high.[2,7]

In some cases of ACC, exclusive steroid precursor secretion with ineffective steroidogenesis can cause tumors to appear nonfunctional if hormonal testing is limited to standard testing for cortisol, aldosterone, or metanephrine overproduction.[3] Using liquid chromatography with tandem mass spectrometry (LC-MS/MS), one study used a 13-steroid panel to evaluate steroids and their precursor levels in 10 cases of ACC compared with pheochromocytomas, cortisol-producing adrenal adenomas, and nonfunctional adenomas.[7] The researchers noted that 11-deoxycortisol was significantly elevated in all cases of ACC, and that a combination of steroid precursors such as 17-OHP, 11-deoxycortisol, 11-deoxycorticosterone, 17-hydroxypregnenolone, and androstenedione, in addition to cortisol and dehydroepiandrosterone sulfate, can further distinguish ACC from non-ACC adrenal masses.[7]

CONCLUSION

ACCs are aggressive tumors with a poor prognosis. Use of steroid precursor hormones can assist in more rapid and accurate diagnosis and serve as tumor markers to evaluate for postoperative recurrence. While some endocrinology guidelines recommend the use of steroid precursor hormones in the evaluation of suspicious adrenal masses, the most sensitive set of precursor hormones to provide the best discrimination between ACC and non-ACC masses has yet to be determined.[2,3,10] ■

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