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Hormonally active adrenocortical carcinoma in a 24-year old woman

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Background	Adrenal tumors are common and frequently identified incidentally; adrenalectomy is indicated for functional tumors, masses ≥4 cm, and cases where malignancy is suspected.
Summary	A 24-year old previously healthy woman presented with a six-month history of weight gain, amenorrhea, hirsutism, acne, and hypertension. Biochemical evaluation revealed hypercortisolism and elevated DHEA-S. Abdominal imaging demonstrated an 11 cm right adrenal mass, abutting the right hepatic lobe, right kidney, and inferior vena cava. The patient underwent open right adrenalectomy for the presumptive diagnosis of hormonally active adrenocortical carcinoma (ACC). The tumor was able to be mobilized from surrounding structures without requiring resection of adjacent organs. Pathological exam demonstrated a 728 g, 16.5 cm ACC with extensive necrosis, and Ki67 proliferation index of 35% and large vessel vascular invasion. Postoperatively, the symptoms of hypercortisolism, virilization, and hypertension resolved. The patient is currently undergoing adjuvant mitotane therapy and has no evidence of disease six months after surgery.
Conclusion	Adrenal masses are highly prevalent and are detected at increasing rates with widespread use of cross-sectional imaging. Biochemical evaluation should be performed to diagnose hormonally active tumors. The majority of adrenal lesions are benign and nonfunctional. Adrenalectomy is indicated for functional tumors, and in cases where malignancy is suspected, and should be considered for masses ≥4 cm. ACCs are rare, often functional tumors with a poor prognosis. Surgical resection is the primary treatment. Adjuvant mitotane may improve survival and should be considered for high-risk tumors. Clinical trials of molecular and immunotherapies are ongoing, but genetic variability and the rarity of these tumors remains a challenge to the development of novel therapeutic options.
Keywords	Adrenal tumor; adrenocortical carcinoma; functional adrenal tumor; adrenal incidentaloma; Cushing syndrome

Case Description

A 24-year old woman presented to her primary care physician with a six-month history of weight gain, accompanied by amenorrhea with new hirsutism and worsening acne (figure 1). She also noted new onset of hypertension. She was initiated on anti-hypertensive therapy, which was escalated during the course of her diagnostic evaluation, but ultimately remained poorly controlled on four anti-hypertensive agents. The patient had previously been a healthy marathon runner and worked full-time. Her past medical history and family history were otherwise unremarkable.

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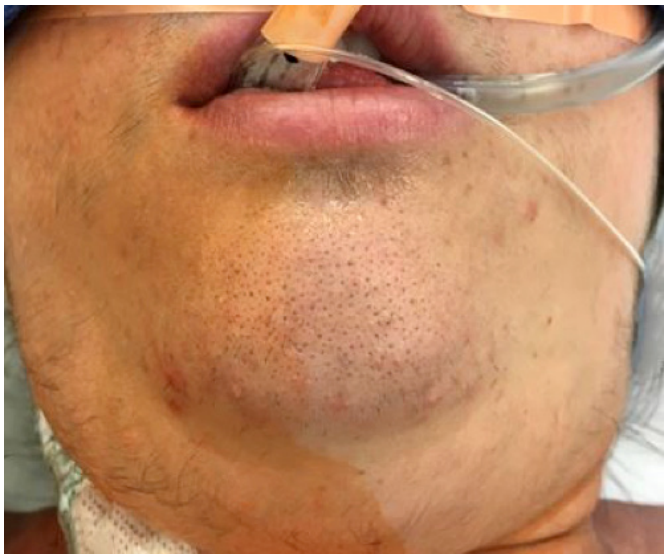

Figure 1. Pre-operative findings of moon facies, hirsutism, and acne.

Biochemical evaluation demonstrated an elevated midnight salivary cortisol of 510 ng/dL (normal <100 ng/dL), suppressed 6:30 AM serum ACTH <1 pg/mL (normal 6–76 pg/mL), elevated DHEA-S of 350 mcg/dL (normal 44–332 mcg/dL), and hypokalemia with serum potassium 2.8 mmol/L (normal 3.4–5.0 mmol/L). Low- and high-dose dexamethasone suppression tests were consistent with autonomous adrenal secretion of cortisol. Serum renin, aldosterone, and metanephrines were within normal limits. A CT scan of the abdomen demonstrated an 11-cm heterogenous right adrenal mass (figure 2), abutting the inferior vena cava (IVC), right kidney, and right hepatic lobe and exerting mass effect on all adjacent structures, without evidence of discrete invasion or distant metastases, and a normal appearing left adrenal gland.

Chest CT did not demonstrate any evidence of pulmonary metastases. On abdominal MRI (not shown), the mass was predominantly mildly T2 hyperintense, with some punctate internal areas of T1 intensity. On postcontrast images, the mass demonstrated heterogenous arterial enhancement and progressive venous enhancement. There was no evidence of concerning lymphadenopathy or distant metastases, and a normal left adrenal gland was visualized.

Imaging and biochemical evaluation were most consistent with a hormonally active adrenocortical carcinoma (ACC). Due to the high concern for malignancy and the large size of the mass, the patient underwent an open right adrenalectomy. Cattell-Braasch and full Kocher maneuvers were performed to expose the adrenal tumor. A cholecystectomy was performed for better access. There was no evidence of direct tumor invasion of the adjacent structures, although neovascularization of the lesion was noted by vessels branching from the right hepatic vein. The mass was able to be mobilized free from the right kidney, IVC, and right hepatic lobe. Final pathologic examination revealed a 728 g, 16.5 cm adrenal-based mass with an orange rim (grossly suggestive of adrenal cortex), with central hemorrhage and necrosis. Surgical margins were negative; no lymph nodes were resected with the specimen.

Microscopically, tumor morphology demonstrated packeted growth, eosinophilic, plasmacytoid cells (often associated with androgen production), and prominent chromatin centers. There was frank tumor necrosis and conspicuous mitoses, including atypical mitoses, and large vessel invasion (not into IVC or renal vein), findings consistent with a malignant diagnosis (figure 3). The tumor was staged as T3NXM0 by current 7th edition American Joint Committee on Cancer staging. Immunohistochemical stains were

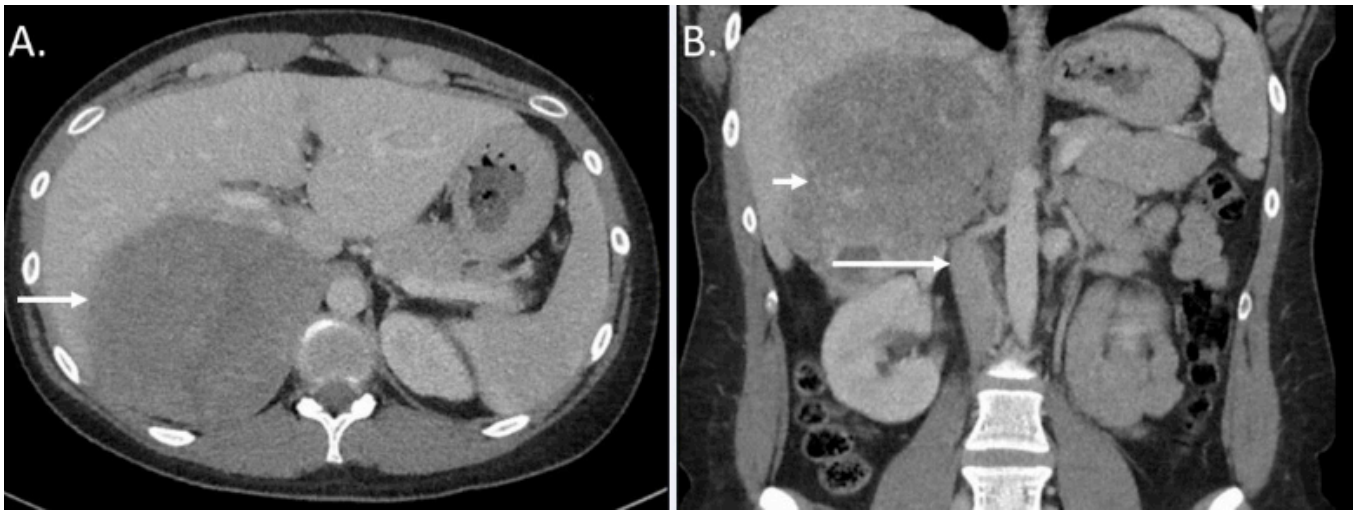

Figure 2. CT abdomen and pelvis with intravenous contrast. A.) Axial images demonstrating an 11 cm, heterogenous adrenal mass (white arrow). B.) Coronal images showing the tumor (short white arrow) abutting the inferior vena cava (long white arrow), right hepatic lobe, and right kidney.

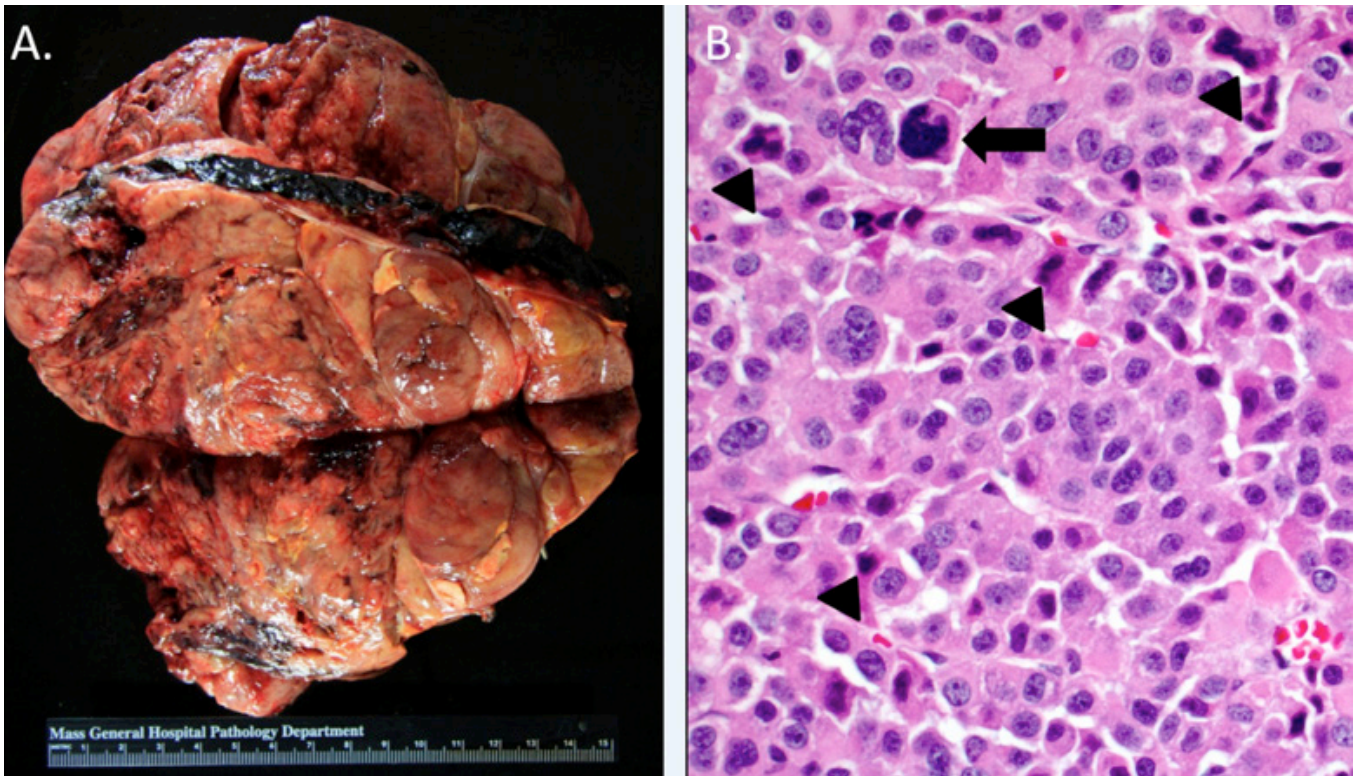

Figure 3. CT abdomen and pelvis with intravenous contrast. A.) Axial images demonstrating an 11 cm, heterogenous adrenal mass (white arrow). B.) Coronal images showing the tumor (short white arrow) abutting the inferior vena cava (long white arrow), right hepatic lobe, and right kidney.

positive for markers associated with adrenal cortical origin, with a markedly elevated Ki67 proliferative index at 35%. Taken together, the findings pointed to a clear diagnosis of ACC.

Postoperatively, the patient did well, and she was discharged home five days later on prednisone, normotensive off all anti-hypertensive medications. Within two weeks of surgery, she had lost more than 10 pounds and her moon facies, acne, and hirsutism resolved. She is currently undergoing mitotane therapy, and has no evidence of disease six months after surgery. Postoperative surveillance with biochemical evaluation of cortisol and ACTH, and cross-sectional imaging is planned every three months.

Discussion

Adrenal tumors are common, affecting up to 6% of patients on autopsy series; the incidence increases with age. The majority of tumors are incidentally identified, and detection rates have increased with the widespread use of cross-sectional imaging.[1] The initial biochemical evaluation of an adrenal mass includes serum metanephrines, cortisol levels, serum renin and aldosterone levels, DHEA-S, electrolyte, and creatinine levels; ultimately most adrenal incidentalomas are benign and nonfunctional.[1-3] Functional adrenal tumors include pheochromocytomas, aldosteronomas, cortisol-producing adenomas, and ACCs. Secondary malignancies metastatic to the adrenals are more frequent than ACCs.

Adrenalectomy is indicated in hormonally active tumors and when malignancy is suspected. Current Endocrine Society (American Association of Clinical Endocrinologists/American Association of Endocrine Surgeons) guidelines suggest considering adrenalectomy for nonfunctional lesions 4 cm or greater, those with rapid increase in size, and masses with imaging characteristics suggestive of malignancy.[2] National Comprehensive Cancer Network (NCCN) guidelines recommend adrenalectomy in intermediate (4–6 cm) size tumors with aggressive features on imaging, while tumors 4–6 cm in size with benign characteristics may be monitored with serial imaging.[4] The European Society of Endocrinology and the European Network for the Study of Adrenal Tumors (ENSAT) guidelines do not suggest a size cut-off for adrenalectomy, but recommend an individualized approach.[5] Laparoscopic adrenalectomy is considered the standard of care in benign and small tumors, although controversy exists regarding the safety and oncologic outcome of laparoscopic resection in large malignant tumors.[6-9]

Primary adrenocortical carcinomas are rare, with an annual incidence of 0.72–1.26 per million.[10, 11] They are among the most aggressive of human cancers, with a five-year survival of 30%–50%.[12, 13] Approximately 60%–80% of ACCs are functional, and they may present with a mixed hormonal picture, most commonly with Cushing syndrome and virilization, as in this patient.[14] Aldosterone-secreting ACCs are rare, and constitute <3% of primary adrenal cancers.[15, 16] Severe Cushing syndrome may clinically mimic hyperaldosteronism, manifesting with hypertension and hypokalemia. In the presence of markedly elevated glucocorticoid levels, cortisol may bind mineralocorticoid receptors, increasing renal excretion of potassium despite normal aldosterone levels.[17] In addition to functional testing, patients with suspected malignant tumors should undergo an appropriate staging evaluation, including imaging to evaluate for pulmonary or other distant metastases, either with chest CT or FDG-PET CT, or both.[18] In lesions where diagnostic uncertainty exists, MRI may be useful in establishing a diagnosis of ACC, as well as evaluating for vascular invasion or tumor thrombus. Although there may be a role for percutaneous biopsy of suspected adrenal metastases in patients with a known cancer history, biopsy should never be performed until functional evaluation has excluded a diagnosis of pheochromocytoma, due to the inherent dangers of manipulating catecholamine-secreting tumors.[19] There is no role for biopsy of suspected ACCs, due to the potential for seeding the biopsy tract.[2]

Surgical resection is the primary therapy for ACC and may be curative in localized disease[13]; however, recurrence rates are high, with five-year recurrence-free survival approximately 20%.[20] Prognostication remains a challenge in ACC. The Weiss score, first introduced in 1984, relies upon nine histologic features and performs well in differentiating between benign adrenocortical neoplasms and ACCs; however its prognostic value is variable.[21] Multiple publications report the strong performance of the Ki67 index as a predictor of both recurrence-free and overall survival.[22-24] Based on retrospective studies and with some conflicting evidence, adjuvant mitotane has been posited to improve recurrence-free and overall survival, and is typically recommended for high-risk tumors.[25, 26] The 2015 NCCN guidelines suggest consideration of adjuvant mitotane for larger or high grade tumors, and those with capsular rupture or positive margins; however given the rarity of ACC, this recommendation is based on retrospective data alone.[4] Mitotane may be used in combination with external beam radiation or other cytotoxic chemotherapies. Clinical trials of molecular and immunotherapies are ongoing, but they have been stymied by genetic variability in these tumors and limited numbers of cases.[27] The NCCN guidelines suggest ongoing post-operative surveillance every 3–6 months with cross-sectional imaging and biochemical evaluation if the tumor was originally functionally active.

Conclusion

Adrenal masses are common and being detected at increasing rates due to widespread use of cross-sectional imaging. Biochemical evaluation should be performed to diagnose hormonally active tumors. The majority of adrenal cortical lesions are benign and nonfunctional. Adrenalectomy is indicated for functional tumors, and cases where malignancy is suspected, and should be considered for masses ≥4 cm. Adrenocortical carcinomas are rare, usually functional, and portend a poor prognosis. Surgical resection is the primary treatment. Adjuvant mitotane may be considered for high-risk tumors. Molecular and immunotherapies have had little success with few in development due to genetic heterogeneity in these rare tumors.

Lessons Learned

Adrenal tumors are common; the majority are benign and nonfunctional. Adrenalectomy is indicated for functional tumors, large masses, and when malignancy is suspected. Adrenocortical carcinomas are rare, typically functional tumors with a poor prognosis. Surgical resection is the primary treatment. Adjuvant mitotane may be considered for high-risk tumors.

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