Radiology Case Reports

Volume 8, Issue 3, 2013

Classic Cushing's syndrome in a patient with adrenocortical carcinoma

Katelyn M. Adkins, BS; James T. Lee, MD; Aaron L. Bress, DO; Susan E. Spires, MD; Cortney Y. Lee, MD; and Andres R. Ayoob, MD

Adrenocortical carcinoma is an aggressive but rare neoplasm of the adrenal cortex, with an estimated incidence of approximately 2.5 per one million patients. Patient prognosis is often very poor. Patients often present with symptoms of hormone hypersecretion but may also present with pain or a palpable mass. Imaging plays an important role in preoperative planning when clinical and biochemical findings are compatible with adrenal cortical carcinoma. We report a case of adrenocortical carcinoma in a young woman who presented with classical Cushing syndrome, but who had an atypical hormonal profile.

Case report

A 20-year-old female presented with classic symptoms of Cushing's syndrome. The patient first noticed symptoms one year earlier. During that year, she complained of a 60-pound weight gain, amenorrhea, hirsutism, acne, bruising, and diffuse striae. Physical examination demonstrated moon facies, "buffalo hump," and diffuse striae (abdomen, hip, buttock, breast, and lower extremity), as well as acne, bruising, and significant hirsutism (Figs. 1A-C).

Biochemical evaluation revealed elevation of both cortisol (serum 26.0 µg/dL, normal range 5-23 µg/dL) and adrenocorticotropin hormone (ACTH) (32 pg/mL, normal range 5-27 pg/mL). Neither cortisol nor ACTH was suppressed by a high- or low-dose dexamethasone suppression test. MRI of the head with and without contrast (performed to evaluate for a potential pituitary adenoma, given the elevated ACTH) revealed a possible microadenoma,

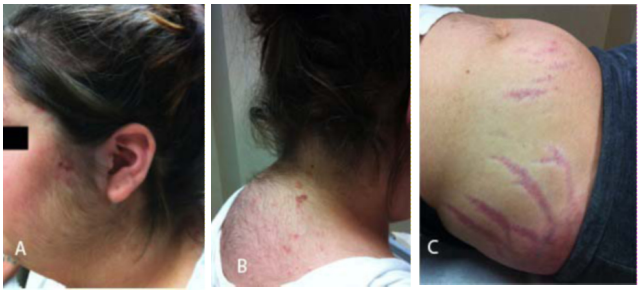

Figure 1. 20-year-old female with Cushing's syndrome. Photographs demonstrate the physical exam findings associated with Cushing's Syndrome. A. Profile illustrates acne and hirsutism. B. Posterior-neck and upper-back view illustrates a typical "buffalo hump" and hirsutism. C. Lateral view of the abdomen illustrates abdominal striae.

although this was felt to be an unlikely source of excess ACTH. Subsequently, a contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis was performed to search for an ectopic source of ACTH production. The CT revealed a 7x4cm, heterogeneous, lobulated, left adrenal mass. Portions of the mass showed poorly defined margins, raising suspicion for local invasion into the retroperitoneal fat (Figs. 2A-C). Contrast enhancement kinetics could not confirm an adrenal adenoma (relative percentage washout [RPW] of 24%), although this examination was not performed for dedicated adrenal mass evaluation (images were obtained at 75 seconds and 3 minutes per a standard abdominal CT protocol versus at 60

Citation: Adkins KM, Lee JT, Bress AL, Spires, SE, Lee, CY, Ayoob AR. Classic Cushing's syndrome in a patient with adrenocortical carcinoma. *Radiology Case Reports*. (Online) 2013;8:826.

Mr. Adkins is in the College of Medicine, Drs. Bress and Ayoob are in the Department of Radiology, Dr. Spires is in the Department of Pathology, and Dr. Lee is in the Department of Surgery, all at the University of Kentucky, Lexington KY. Contact Dr. Lee at jtlee3@uky.edu.

Competing Interests: The authors have declared that no competing interests exist.

DOI: 10.2484/rcr.v8i3.826

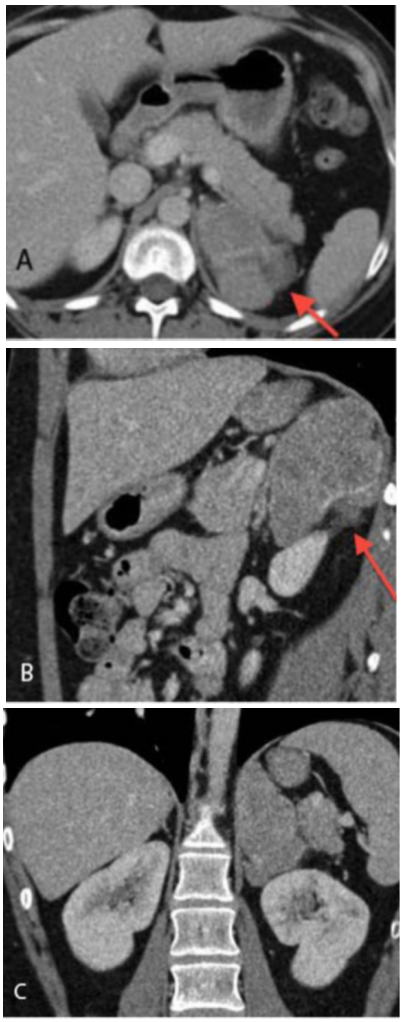

Figure 2. 20-year-old female with Cushing's syndrome. Abdominal CT images were obtained in the axial (A), sagittal (B), and coronal (C) planes, 75 seconds after the administration of IV contrast. A heterogeneously enhancing mass measuring 8x4.5x7cm arose from the left adrenal gland. Portions of the mass had ill-defined borders, and there was suggestion of invasion into the retroperitoneal fat at the posterior margin of the lesion (arrow). There was no evidence for invasion of the adjacent pancreas or kidney.

seconds and 15 minutes per a dedicated adrenal mass protocol). Given the size of the mass and clinical findings of hormonal hypersecretion, adrenal cortical carcinoma was the favored diagnosis. The right adrenal gland was normal, and there was no imaging evidence for distant metastasis within the chest, abdomen, or pelvis.

Given the presence of an adrenal mass, additional biochemical evaluation was ordered; it revealed elevation of dehydroepiandrosterone sulfate (DHEA-S) (697 ug/dL, normal range 145-395 ug/dL). Elevation of multiple adrenal products, especially the sex hormone precursors DHEA-S and testosterone, also raised suspicion for carcinoma. Metanephrines, prolactin, growth hormone, luteinizing hormone, and follicle-stimulating hormone were normal.

The patient underwent open surgery with en bloc resection of the tumor. An elongated, lobulated, left adrenal mass weighing 136g was removed (Fig. 3). Afterward, the patient's cortisol, DHEA, and ACTH levels returned to normal. Histopathological evaluation of the specimen demonstrated an adrenal neoplasm with two large nodular foci of extension into the surrounding fat. Grossly, the tumor was friable, beige-tan, with areas of pale yellow necrosis. On light microscopy, the vast majority of the tumor showed a lobular-to-solid growth pattern with deeply eosinophilic cytoplasm (Fig. 4a). A few vacuolated foci were present (Fig. 4b). The adrenocortical carcinoma (ACC) showed extensive infiltration into the adjacent fat (Fig. 4c). Marked cytologic atypia was noted, with nuclear enlargement and pleomorphism. Lipofuchsin pigment, typical for hormonally active tumors, was easily discernible. Pathologically, a tumor is defined as ACC when three of the fol-

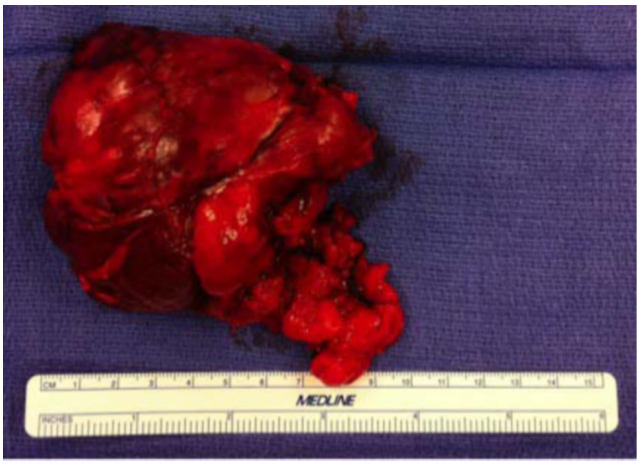

Figure 3. 20-year-old female with Cushing's syndrome. Gross specimen.

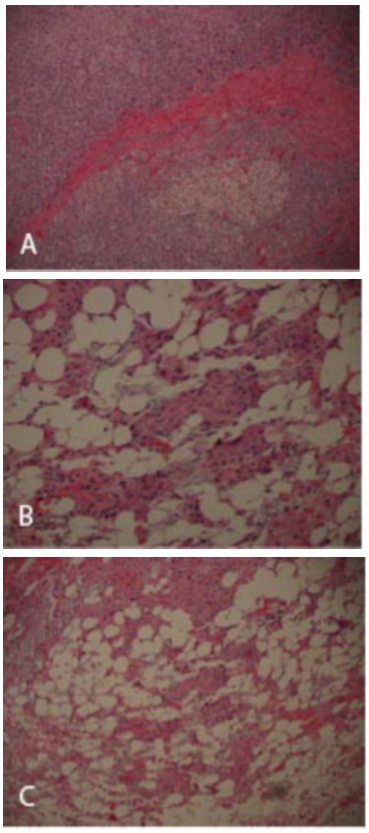

Figure 4. 20-year-old female with Cushing's syndrome. On light microscopy, the vast majority of the tumor showed a lobular-to-solid growth pattern with deeply eosinophilic cytoplasm (A). A few vacuolated foci were present (B). The adrenocortical carcinoma (ACC) showed extensive infiltration into fat (C), and large nodular foci were present in separately submitted periadrenal soft tissue.

lowing histologic criteria are met: 1) high nuclear grade, 2) mitotic rate > 5 per 50 high-power fields, 3) atypical mitoses, 4) clear cells < 25%, 5) diffuse architectural pattern in more than one-third of the tumor, 6) confluent necrosis, 7) venous invasion, 8) sinusoidal invasion, and 9) capsular invasion (1). This tumor fulfilled five of the criteria. Curiously, despite the aggressive pattern of invasion, mitotic figures were less than 5/50 hpf, and no atypical mitoses were noted.

The invasion into surrounding tissue, in addition to the size of the tumor, indicated a stage III ACC. After surgery, the patient underwent 45 days of adjuvant external-beam radiation. The etiology of the elevated ACTH levels in the setting of ACC remains unclear. Furthermore, the tumor did not stain for ACTH (Fig. 5).

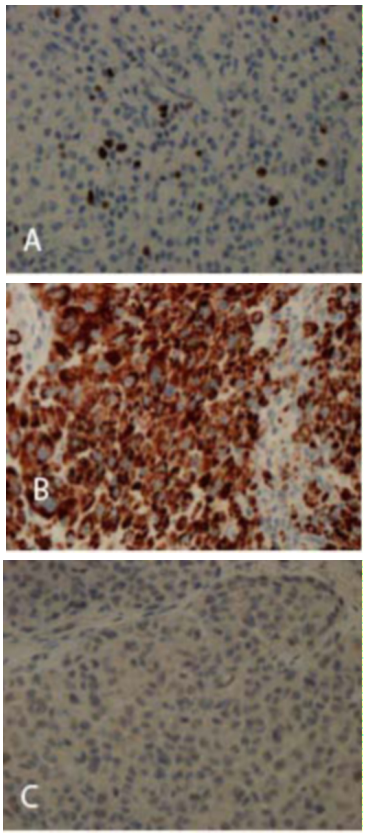

Figure 5. 20-year-old female with Cushing's syndrome. The tumor showed strong positivity for Melan A (A) and sparse positivity for synaptophysin but was negative for chromogranin. Multiple blocks were stained for ACTH, all with negative findings (B). A Ki-67 showed 4.5 % positivity (C).

One year following surgery, the patient has returned to her baseline weight with near-complete resolution of her Cushingoid habitus and hirsutism, and a return of menstruation. Followup abdominal and pelvic CT 11 months after surgery revealed no evidence of local recurrence or distant metastasis.

Discussion

Patients with adrenocortical carcinoma (ACC) commonly present in one of three clinical patterns. In approximately 10% of patients, an adrenal mass is discovered incidentally in an asymptomatic patient (adrenal incidentaloma). Approximately 30% of patients present with symptoms of a mass or mass effect but without clinical findings of hypersecretion. The most common presentation, however, is one of overt clinical symptoms suggesting hormone hypersecretion of the adrenal gland. This pattern accounts for 60% of cases and is more common in women under 40 years of age (2). Hypersecretion from an ACC accounts for 5-10% of cases of Cushing's syndrome. The majority of cases are corticotrophin-dependent, with the pituitary gland being the most common source of ACTH hypersecretion (80%). 10% of cases occur as a result of ectopic ACTH secretion (from a small-cell carcinoma, for instance), while the remaining 10% of cases are corticotropin-independent (3). Adrenocortical tumors are the most common cause of corticotropin-independent Cushing's syndrome (4, 5).

A hormonal workup is essential before surgery is considered. At least 3 of 4 glucocorticoid tests should be performed. Glucocorticoid tests include measurements of plasma ACTH, serum cortisol, 24-hour free urinary cortisol, and a dexamethasone suppression test (1mg, 2300 h) (6). Measuring serum levels of sexual steroids and their precursors (DHEA-S, testosterone, androstendione) and/or mineralocorticoids may indicate an adrenal malignancy and determine the approach to treatment (6).

Imaging is essential in the diagnosis and pretreatment staging of patients with suspected ACC. Magnetic resonance imaging (MRI) and CT are the imaging modalities of choice to localize a source of hormonal hypersecretion as well as to assess for local invasion and distant metastasis (7). Imaging may also be useful in distinguishing an adrenal adenoma (benign lesion) from an ACC. The size of an adrenal mass is one of the best indicators of malignancy. Adrenal adenomas are usually small (< 6 cm, typically between 2 and 3 cm). Masses measuring 6 cm or greater have a higher rate of malignancy (~ 25%) and should be resected (6). Adenomas are typically homogeneous; heterogeneity (often due to necrosis and/or hemorrhage) suggests malignancy. A subset of adrenal adenomas have a high lipid content (lipid-rich adenomas) and can be reliably diagnosed on unenhanced CT (< 10 Hounsfield units) (8) and dual-phase gradient-echo MRI (signal loss on out-of-phase gradient-echo images relative to in-phase gradien-echo images) (9, 10). Both adenomas and ACC enhance following administration of intravenous contrast material. ACC typically enhances heterogeneously, while adenomas are typically more homogeneous. Moreover, although heterogeneity and large size are more reliable indicators of malignancy, assessment of the temporal pattern of contrast enhancement has also been described. Studies of contrast kinetics have shown that adrenal adenomas demonstrate more rapid de-enhancement (or "washout" of intravenous contrast material) relative to nonadenomatous adrenal lesions (such as ACC) (11, 12). Caoili et al (13) have described a CT protocol consisting of images obtained during three distinct phases: before administration of contrast material (unenhanced), at a 50- to 80-sec delay following administration of contrast material (enhanced), and at a 15-min delay after administration of contrast material (de-

layed contrast-enhanced). Using this protocol, the degree of "washout" can be quantified as an absolute percentage washout (APW = [enhanced attenuation – delayed attenuation]/[enhanced attenuation – unenhanced attenuation]) or, if unenhanced images are not available, as a relative percentage washout (RPW = [enhanced attenuation – delayed attenuation]/enhanced attenuation) (8, 11). Adenomas typically demonstrate rapid washout, which is defined as an APW of more than 60% and an RPW of more than 40% on delayed images. Studies of the contrast kinetics of ACC have shown that these lesions typically have a RPW of <40% (11). Ill-defined margins and local invasion are additional imaging features suggestive of malignancy.

If malignancy is suspected preoperatively, an open surgical approach is the standard of care, given the aggressive nature and high local recurrence of this disease. In the evaluation of an adrenal mass, imaging findings are arguably the most important factor used to dictate surgical approach (open, laparoscopic, versus retroperitoneoscopic). Considerations include size, aggressive appearance on imaging, and involvement of the surrounding structures. Complete tumor resection with surrounding fatty/nodal tissue is indicated in all but stage IV disease (14-17). Extensive surgery with resection of invaded tissues may be required. It is crucial to avoid tumor spillage by maintenance of the tumor capsule (2).

In addition to surgery, Mitotane may be used to treat or control ACC. Mitotane is a cytotoxic drug that specifically targets adrenocortical cells. Hahner and Fassnacht found that treatment with Mitotane caused regression of ACC tumors in 25% of cases and was beneficial in controlling hormone levels in most patients (18). Radiation therapy is also performed palliatively for metastasis and locally advanced disease (19). Most recently, it has been found that the insulin-like growth factor (IGF) signaling pathway is thought to be important in the development and growth of ACC. The IGF pathway is activated by interactions between the circulating growth factors IGF-1 and IGF-2 and their membrane-bound receptor, IGF-1R. A number of agents are being developed that target this pathway by blocking the ability of IGF-1 and IGF-2 to bind to and activate IGF-1R. One such agent is a monoclonal antibody called IMC-A12 (cixutumumab), with clinical trials sponsored by the NCI under way. Rosiglitazone is another important therapeutic drug targeting the IFG 2 receptor (20).

References

1. Hironubu S, Takashi S, Yasuhiro N. Discerning malignancy in resected adrenocortical tumors. *Expert Opin Med Diagn.* 2008; 2(10): 1095-105. [PubMed]
2. Proye C, Armstrong J, Pattou F. Adrenocortical carcinoma: Nonfunctioning and functioning. In: Clark O, Duh Q, Kebebew E. 2nd ed. *Textbook of endocrine surgery.* Philadelphia, PA: Elsevier; 2005: 612-618.
3. Favia G, Lumachi F, Iacobone M. Cushing's syndrome. In: Clark O, Duh Q, Kebebew E. *Textbook of endocrine surgery.* 2nd ed. Philadelphia, PA; 2005: 612-618.
4. Orth D, Kovacs W, DeBold C. The adrenal cortex. In: Wilson J, Foster D. T*extbook of endocrinology*. 8th ed. Philadelphia: Saunders; 1992: 489-619.
5. Bertagna C, Orth D. Clinical and laboratory findings and results of therapy in 58 patients with adrenocortical tumors admitted to a single medical center (1951 to 1978). *Am J Med* 1981; 71: 855-875. [PubMed]
6. National Institutes of Health 2002 NIH state-of-the-science statement on management of the clinically inapparent adrenal mass ("incidentaloma"). *NIH Consens State Sci Statements* 19:1-25. [PubMed]
7. Niederle B, Heinz-Peer G, Kaczirek K, Kurtaran A. The value of adrenal imagining in adrenal surgery. In: Linos D, van Heerden J. *Adrenal glands: Diagnostic aspects and surgical therapy*. Springer; 2005: 41-56.
8. Pena C, Boland G, Han P, Lee M, Mueller P. Characterization of indeterminate (lipid-poor) adrenal masses: use of washout characteristics at contrast-enhanced CT. *Radiology* 2000; 217: 798-802. [PubMed]
9. Bilbey J, McLoughlin R, Kurkjian P, et al. MR imaging of adrenal masses: value of chemical-shift imaging for distinguishing adenomas from other tumors. *American Journal of Roentgenology* 1995; 164:637-642. [PubMed]
10. Savci G, Yazici Z, Sahin N, Akgoz S, Tuncel E. Value of chemical shift subtraction MRI in characterization of adrenal masses. *American Journal of Roentgenology* 2006; 186:1 130-135. [PubMed]
11. Szolar D, Korobkin M, Reittner P, et al. Adrenocortical carcinomas and adrenal pheochromocytomas: mass and enhancement loss evaluation at delayed contrast-enhanced CT. *Radiology* 2005; 234 (2):479–485. [PubMed]
12. Slattery J, Blake M, Kalra M, et al. Adrenocortical carcinoma: contrast washout characteristics on CT. *American Journal of Roentgenology* 2006; 187:1 W21-W24. [PubMed]
13. Caoili EM, Korobkin M, Francis IR, Cohan RH,Dunnick NR. Delayed enhanced CT of lipid-poor adrenal adenomas. *American Journal of Roentgenology* 2000; 175:1411-5. [PubMed]
14. Dackiw A, Lee J, Gagel R, Evans D. Adrenal cortical carcinoma. *World J Surg* 2001; 25: 914-926. [PubMed]
15. Icard P, Chapuis Y, Andreassian B, Bernard A, Proye C. Adrenocortical carcinoma in surgically treated patients: a retrospective study on 156 cases by the French Association of Endocrine Surgery. *Surgery* 1992; 112: 972-980. [PubMed]
16. Lee J, Berger D, el-Naggar A, et al. Surgical management, DNA content, and patient survival in adrenal cortical carcinoma. *Surgery* 1995; 118(6): 1090-1098. [PubMed]
17. Allolio B. Clinical review: Adrenocortical carcinoma: Clinical update. *Journal of Clinical Endocrinology & Metabolism*. 2006; 91(6):2027–2037. [PubMed]
18. Hahner S, Fassnacht M. Mitotane for adrenocortical carcinoma treatment. *CurrOpinInvestig Drugs* 2005; 6: 386-394. [PubMed]

19 Percarpio B, Knowlton A. Radiation therapy of adrenal cortical carcinoma. *Acta Radiol Ther Phys Biol* 1976; 15:288–29. [PubMed]

20. Cantini G, Lombardi A, Piscitelli E, et al. Rosiglitazone inhibits adrenocortical cancer cell proliferation by interfering with the IGF-IR intracellular signaling. *PPAR Research*. 2008 Article ID 904041. [PubMed]