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, 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
seconds and 15 minutes per a dedicated adrenal mass pro-
tocol. 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 bio-
chemical evaluation was ordered; it revealed elevation of
dehydroepiandrosterone sulfate (DHEA-S) (697 ug/dL,
normal range 145-395 ug/dL). Elevation of multiple adre-
nal products, especially the sex hormone precursors
DHEA-S and testosterone, also raised suspicion for carci-
noma. Metanephrines, prolactin, growth hormone, luteiniz-
ing hormone, and follicle-stimulating hormone were
normal.

The patient underwent open surgery with en bloc resec-
tion 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 tu-
mor was friable, beige-tan, with areas of pale yellow necro-
isis. On light microscopy, the vast majority of the tumor
showed a lobular-to-solid growth pattern with deeply eosin-
ophilic 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 enlarge-
ment and pleomorphism. Lipofuscin pigment, typical for
hormonally active tumors, was easily discernible. Pathol-
ogically, a tumor is defined as ACC when three of the fol-

Figure 2. 20-year-old female with Cushing’s syndrome. Abdominal
CT images were obtained in the axial (A), sagittal (B), and co-
ronal (C) planes, 75
seconds after the
administration of IV
contrast. A heteroge-
neously enhancing
mass measuring
8x4.5x7cm arose from
the left adrenal gland.
Portions of the mass
had ill-defined bor-
ders, and there was
suggestion of invasion
into the retroperito-
neal fat at the poste-
rior margin of the
lesion (arrow). There
was no evidence for
invasion of the adja-
cent pancreas or
kidney.

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

Figure 4. 20-year-old female with Cushing’s syndrome. On light mi-
croscopy, the vast major-
ity of the tumor showed a
lobular-to-solid growth
pattern with deeply eosin-
ophilic cytoplasm (A). A
few vacuolated foci were
present (B). The adreno-
cortical carcinoma (ACC)
showed extensive infiltra-
tion into fat (C), and
large nodular foci were
present in separately
submitted periadrenal
soft tissue.
Classic Cushing’s syndrome in a patient with adrenocortical carcinoma

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 gradient-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). Caoli 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-second delay following administration of contrast material (enhanced), and at a 15-min delay after administration of contrast material (de-
An important therapeutic drug targeting the IGF-2 receptor is called IMC-A12 (cixutumumab), with clinical trials sponsored by the NCI under way. Rosiglitazone is another inhibitor of the IGF pathway that targets the 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 blocking the ability of IGF-1 and IGF-2 to bind to and activate IGF-1R. One such agent is a monoclonal antibody blocking the ability of IGF-1 and IGF-2 to bind to and activate IGF-1R. One such agent is a monoclonal antibody blocking the ability of IGF-1 and IGF-2 to bind to and activate IGF-1R.

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 IGF-2 receptor (20).

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