APPROACH TO THE PATIENT: INCIDENTALLY DISCOVERED ADRENAL MASS

Epidemiology Incidentally discovered adrenal masses, commonly termed adrenal "incidentalomas," are common, with a prevalence of at least 2% in the general population as documented in CT and autopsy series. The prevalence increases with age, with 1% of 40-year-olds and 7% of 70-year-olds harboring an adrenal mass.

Etiology Most solitary adrenal tumors are monoclonal neoplasms. Several genetic syndromes, including MEN 1 (*MEN1*), MEN 2 (*RET*), Carney's complex (*PRKAR1A*), and McCune-Albright (*GNAS1*), can have adrenal tumors as one of their features. Somatic mutations in *MEN1, GNAS1*, and *PRKAR1A* have been identified in a small proportion of sporadic adrenocortical adenomas. Aberrant expression of membrane receptors (gastric inhibitory peptide, α- and β-adrenergic, luteinizing hormone, vasopressin V1, and interleukin 1 receptors) have been identified in some sporadic cases of macronodular adrenocortical hyperplasia.

The majority of adrenal nodules are endocrine-inactive adrenocortical adenomas. However, larger series suggest that up to 25% of adrenal nodules are hormonally active, due to a cortisol- or aldosterone-producing adrenocortical adenoma or a pheochromocytoma associated with catecholamine excess (Table 406-5). Adrenocortical carcinoma is rare but is the cause of an adrenal mass in 5% of patients. However, the most common cause of a malignant adrenal mass is metastasis originating from another solid tissue tumor (Table 406-5).

Differential Diagnosis and Treatment Patients with an adrenal mass >1 cm require a diagnostic evaluation. Two key questions need to be addressed: (1) Does the tumor autonomously secrete hormones that could have a detrimental effect on health? (2) Is the adrenal mass benign or malignant?

Hormone secretion by an adrenal mass occurs along a continuum, with a gradual increase in clinical manifestations in parallel with hormone levels. Exclusion of catecholamine excess from a pheochromocytoma arising from the adrenal medulla is a mandatory part of the diagnostic workup (Fig. 406-13). Furthermore, autonomous cortisol and aldosterone secretion resulting in Cushing's syndrome or primary aldosteronism, respectively, require exclusion. Adrenal incidentalomas can be associated with lower levels of autonomous cortisol secretion, and patients may lack overt clinical features of Cushing's syndrome. Nonetheless, they may exhibit one or more components of the metabolic syndrome (e.g., obesity, type 2 diabetes, or hypertension). There is ongoing debate about the optimal treatment for these patients with mild or subclinical Cushing's syndrome. Overproduction of adrenal androgen precursors, DHEA and its sulfate, is rare and most frequently seen in the context of adrenocortical carcinoma, as are increased levels of steroid precursors such as 17-hydroxyprogesterone.

For the differentiation of benign from malignant adrenal masses, imaging is relatively sensitive, although specificity is suboptimal. CT is the procedure of choice for imaging the adrenal glands (Fig. 406-11). The risk of adrenocortical carcinoma, pheochromocytoma, and benign adrenal myelolipoma increases with the diameter of the adrenal mass. However, size alone is of poor predictive value, with only 80% sensitivity and 60% specificity for the differentiation of benign from malignant masses when using a 4-cm cut-off. Metastases are found with similar frequency in adrenal masses of all sizes. Tumor density on unenhanced CT is of additional diagnostic value, with most adrenocortical adenomas being lipid rich and thus presenting with low attenuation values (i.e., densities of <10 HU). By contrast, adrenocortical carcinomas, but also pheochromocytomas, usually have high attenuation values (i.e., densities >20 HU on precontrast scans). Generally, benign lesions are rounded and homogenous, whereas most malignant lesions appear lobulated and inhomogeneous. Pheochromocytoma and adrenomyelolipoma may also exhibit lobulated and inhomogeneous features. Additional information can be obtained from CT by assessment of contrast wash-out after 15 min, which is >50% in benign lesions but <40% in malignant lesions, which usually have a more extensive vascularization. MRI also allows for the visualization of the adrenal glands with somewhat lower resolution than CT. However, because it does not involve exposure to ionizing radiation, it is preferred in children, young adults, and during pregnancy. MRI has a valuable role in the characterization of indeterminate adrenal lesions using chemical shift analysis, with malignant tumors rarely showing loss of signal on opposed-phase MRI.

Fine-needle aspiration (FNA) or CT-guided biopsy of an adrenal mass is almost never indicated. FNA of a pheochromocytoma can cause a life-threatening hypertensive crisis. FNA of an adrenocortical carcinoma violates the tumor capsule and can cause needle track metastasis. FNA should only be considered in a patient with a history of nonadrenal malignancy and a newly detected adrenal mass, after careful exclusion of pheochromocytoma, and if the outcome will influence therapeutic management. It is important to recognize that in 25% of patients with a previous history of nonadrenal malignancy, a newly detected mass on CT is not a metastasis.

Adrenal masses associated with confirmed hormone excess or suspected malignancy are usually treated surgically (Fig. 406-13) or, if adrenalectomy is not feasible or desired, with medication. Preoperative exclusion of glucocorticoid excess is particularly important for the prediction of postoperative suppression of the contralateral adrenal gland, which requires glucocorticoid replacement peri- and postoperatively. If the initial decision is for observation, imaging and biochemical testing should be repeated about a year after the first assessment. However, this may be performed earlier in patients with borderline imaging or hormonal findings. There is no agreement with regard to the required long-term follow-up beyond 1 year in patients with normal biochemistry and no evidence of increased tumor size at follow-up.

TABLE 406-5 CLASSIFICATION OF UNILATERAL ADRENAL MASSES

Mass	Approximate Prevalence (%)
Benign	
Adrenocortical adenoma	
Endocrine-inactive	60–85
Cortisol-producing	5–10
Aldosterone-producing	2–5
Pheochromocytoma	5–10
Adrenal myelolipoma	<1
Adrenal ganglioneuroma	<0.1
Adrenal hemangioma	<0.1
Adrenal cyst	<1
Adrenal hematoma/hemorrhagic infarction	<1
Indeterminate	
Adrenocortical oncocytoma	<1
Malignant	
Adrenocortical carcinoma	2–5
Malignant pheochromocytoma	<1
Adrenal neuroblastoma	<0.1
Lymphomas (including primary adrenal lymphoma)	<1
Metastases (most frequent: breast, lung)	15

Note: Bilateral adrenal enlargement/masses may be caused by congenital adrenal hyperplasia, bilateral macronodular hyperplasia, bilateral hemorrhage (due to antiphospholipid syndrome or sepsis-associated Waterhouse-Friderichsen syndrome), granuloma, amyloidosis, or infiltrative disease including tuberculosis.

ADRENOCORTICAL CARCINOMA

Adrenocortical carcinoma (ACC) is a rare malignancy with an annual incidence of 1–2 per million population. ACC is generally considered a highly malignant tumor; however, it presents with broad interindividual variability with regard to biologic characteristics and clinical behavior. Somatic mutations in the tumor-suppressor gene *TP53* are found in 25% of apparently sporadic ACC. Germline *TP53* mutations are the cause of the Li-Fraumeni syndrome associated with multiple solid organ cancers including ACC and are found in 25% of pediatric