Adrenal Tumors in Adults

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KEYWORDS

• Adrenal • Adrenal adenoma • Adrenocortical carcinoma • Pheochromocytoma

ABSTRACT

Although most adrenal tumors are not diagnostic dilemmas, there are cases that are challenging. This may be due to the tissue provided, for example fragmented tissue received in the setting of morcellation, or it may be due to inherently challenging histology, such as in cases with equivocal features of malignancy. Additionally, much has been learned about the molecular alterations of adrenal tumors, especially pheochromocytomas. Many of these alterations represent germline mutations with significant clinical implications for patients and their families. The aim of this review is to provide an overview of the most common adrenal tumors in adults so that pathologists can tackle these interesting tumors.

OVERVIEW

This article will present an overview of the most common adrenal tumors in adults. It will start with a discussion of adrenal incidentalomas, including what they represent and when they are removed. Next adrenal cortical adenomas, the most common adrenal neoplasm, and a tumor that is generally diagnostically straight-forward will be covered. From there adrenocortical carcinomas will be reviewed, concentrating on gross and microscopic findings and histologic features of malignancy. The article will finish with pheochromocytomas, addressing not only what they look like, but also discussing important hereditary associations.

ADRENAL INCIDENTALOMA

Adrenal incidentalomas are defined as adrenal masses larger than 1 cm that are inadvertently discovered in the course of diagnostic evaluation or treatment of another medical condition.[1] This excludes masses found in the setting of imaging performed to detect metastatic disease in a patient with a known malignancy since 75% of such masses are metastases.[2] Adrenal incidentalomas are estimated to be present in 1.5% to 9.0% of people and are found in up to 5.0% of patients undergoing computed tomography of the abdomen.[3] In general, the lesions are small (<3–4 cm), men and women are equally affected, and they are most commonly detected in patients in their sixth decade of life.[4] A list of underlying lesions responsible for incidentalomas is presented in **Table 1**.[1] There are 2 main factors to consider when deciding whether an incidentaloma should be surgically removed. The first is the functional status of the tumor, and the second is the risk of malignancy. Roughly 10% of incidentalomas are functional and fewer than 5% are malignant (see **Table 1**).[1] A 2002 National Institutes of Health state-of-the-science statement regarding the management of patients with incidentalomas elaborated the following abbreviated conclusions.[2] Patients with biochemical evidence of a pheochromocytoma should be surgically treated. Additionally, surgery should be considered for patients with clinically apparent functional cortical tumors. Data were deemed insufficient to advocate for surgery or nonsurgical management of tumors with subclinical hyperfunctioning adrenal cortical adenomas. Because of the higher risk of malignancy with increased tumor size (adrenal cortical carcinomas account for <2% of tumors that are $\leq$4 cm, 6% of tumors that are 4.1–6 cm, and 25% of those >6 cm), it was advised that tumors larger than 6 cm should be surgically removed, those smaller than 4 cm could be followed, and those 4 to 6 cm require additional clinical data to determine whether surgery is appropriate.

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Table 1
Etiology of incidentalomas

Cause	Prevalence, %, Approximate
Adrenal cortical adenoma	80
Functional	10
Adrenal cortical carcinoma	2
Pheochromocytoma	3
Metastases	1
Other causes[a]	15%

[a] Includes adrenal cortical nodules, adrenal cysts, myelolipomas, hematomas/hemorrhage, infection.

Data from Cawood TJ, Hunt PJ, O'Shea D, et al. Recommended evaluation of adrenal incidentalomas is costly, has high false-positive rates and confers a risk of fatal cancer that is similar to the risk of the adrenal lesion becoming malignant; time for a rethink? Euro J Endocrinol 2009;161(4):513–27.

ADRENAL CORTICAL ADENOMA

When evaluating an adrenal cortical adenoma, it is helpful to know the functional status of the tumor. Tumors that produce aldosterone are almost always benign; whereas, production of sex steroids is an ominous sign because there are only rare reports of benign adenomas with sex steroid production. Production of glucocorticoids is seen with adenomas and carcinomas, although because of the much higher frequency of adrenal adenomas compared with adrenal cortical carcinoma, the vast majority of tumors that produce cortisol will be adenomas. Most adenomas are small (<5 cm) and solitary. Grossly, most adenomas are yellow, solid, homogeneous, and well circumscribed (**Fig. 1**A). Some tumors may appear heterogeneous depending on variable cytoplasmic lipid content of tumor cells: a brighter yellow color is seen with higher cytoplasmic lipid and a more tan color with lipid depletion. Secondary changes, such as cystic degeneration and hemorrhage, also can occur (see **Fig. 1**B). Grossly, aldosterone-producing tumors may be slightly brighter yellow ("canary yellow") compared with cortisol-producing tumors. Rarely, cortisol-producing adenomas can be dark or even black in color (see **Fig. 1**C). Ultimately, functional status cannot be determined with certainty by gross evaluation.

Histologically, most adenomas are well circumscribed with a pushing border; however, in some cases a thin fibrous capsule is present (**Fig. 2**A). Most adenomas are similar in appearance to the zona fasciculata (see **Fig. 2**B). The architecture is generally nested or alveolar and less frequently corded or trabecular. The cells are slightly larger than those of fasciculata, but have the same vacuolated clear cytoplasm, small nuclei, and variably distinct nucleoli. The vacuolated cytoplasm is secondary to the high lipid content, which can be demonstrated by an oil-red-O stain. Some tumors have a more heterogeneous microscopic appearance (see **Fig. 2**C). Adenomas associated with aldosterone production are predominantly composed of cells similar to fasciculata; however, some tumors may have populations of cells that appear like fasciculata, glomerulosa, and reticularis admixed. Tumors resected in the setting of spironolactone treatment for an aldosterone-producing adenoma may demonstrate "spironolactone bodies," which are cytoplasmic laminated inclusions composed of aldosterone seen in compact cells with eosinophilic cytoplasm (glomerulosa-like cells of the adenoma) (see **Fig. 2**D). Adenomas associated with cortisol production are often also composed of cells similar to fasciculata, but again there may be some heterogeneity with lipid-depleted cells admixed. Lipofuscin pigment is often present in these lipid-depleted cells (see **Fig. 2**E), and abundant lipofuscin explains the black adenomas described previously. Functional status cannot be determined with certainty with histologic evaluation. However, tumors associated with cortisol production more frequently have intracytoplasmic lipofuscin and myelolipomatous metaplasia, whereas spironolactone bodies are virtually diagnostic of spironolactone treatment, and thus an aldosterone-producing adenoma. Additionally, non-neoplastic cortical atrophy can often be discerned with cortisol-producing adenomas. In contrast, the cortex adjacent to aldosterone-producing adenomas may be normal or even show hyperplasia of the glomerulosa layer ("paradoxic hyperplasia") with the normally patchy glomerulosa layer forming a thick band beneath the adrenal capsule. Scattered cells or small clusters with marked nuclear atypia (Fuhrman nuclear grade 3 or 4) can be seen in benign adenomas regardless of functional status (see **Fig. 2**F). This atypia alone does not warrant a diagnosis of malignancy. In contrast, mitoses are very rarely seen in adenomas (<1 mitosis/50 high-power fields [HPFs] is typical), and atypical mitoses are virtually confined to carcinomas.

Adrenal cortical adenomas are not typically a diagnostic dilemma; however, occasionally, distinguishing an adenoma from a non-neoplastic adrenal cortical nodule or even normal cortex can be a challenge. Non-neoplastic adrenal cortical nodules are frequently seen in the setting of old age, hypertension, and diabetes. These nodules are