Approach to Fine Needle Aspiration of Adrenal Gland Lesions

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Abstract: Adrenal gland lesions are present in 1% to 5% of patients and are most commonly identified incidentally on abdominal imaging. Fine needle aspiration (FNA) cytology plays an important role in the initial workup of adrenal gland nodules, especially in patients with a known history of malignancy. The most common reason for adrenal gland FNA is to differentiate benign adrenal lesions, such as adrenal cortical adenoma, from metastatic malignancy. However, there is a significant cytomorphologic overlap between primary and metastatic adrenal neoplasms. This review focuses on the current state of adrenal gland FNA cytology, with an emphasis on distinguishing adrenocortical adenoma from carcinoma and adrenal cortical neoplasms from metastatic malignancies. The role of immunohistochemistry in specifically diagnosing adrenal neoplasms is discussed. Proposed diagnostic classification systems for adrenal gland FNA cytology are also described.

Key Words: adrenal gland, metastatic carcinoma, fine needle aspiration cytology

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The adrenal glands are paired endocrine organs located in the retroperitoneum, immediately adjacent and superior to the kidneys, surrounded by adipose tissue and fascia.[1–3] Normal adrenal glands weigh <4 g and measure <4 cm in greatest dimension. The adrenal gland is composed of an outer cortex and a smaller inner medulla. The cortex is golden yellow and composed of 3 layers, each producing unique hormones: the outermost zona glomerulosa (mineralcorticoids), the middle zona fasciculata (glucocorticoids), and the innermost zona reticularis (sex hormones). The medulla is red-gray and produces catecholamines.

Primary malignancies of the adrenal gland are rare, with an annual incidence of ~1 per million.[4] However, secondary involvement by extra-adrenal cancers is more common. At autopsy, adrenal metastasis is common by lung (42%) and breast (58%) primary carcinomas.[5–7] Metastatic melanoma (50%) also frequently involves the adrenals.[5] Carcinomas of the gastrointestinal, pancreatobiliary tract, and genitourinary tract can also involve the adrenal glands through distant metastasis or direct extension. In addition, although primary malignancies of the adrenal glands are uncommon, non-neoplastic and benign lesions of the adrenal gland are often identified on imaging for extra-adrenal disease.[3,8–10] Incidental adrenal nodules ("incidentalomas") are present in 1% to 5% of patients. Adrenocortical adenomas are the most common cause of adrenal incidentaloma. Neoplasms of the adrenal medulla (eg, pheochromocytoma) are less common.

This review will cover the role of fine needle aspiration (FNA) in the diagnosis and management of adrenal lesions, with a focus on common entities and diagnostic challenges. The use of ancillary immunohistochemistry in adrenal gland lesions is discussed. Finally, recently proposed classification systems for adrenal gland FNA cytology are described and compared.

IMAGING FINDINGS AND THE APPROACH TO FINE NEEDLE ASPIRATION SAMPLING OF THE ADRENAL GLANDS

The most common indication for FNA of the adrenal gland is to determine the origin of adrenal nodules discovered during abdominal computed tomographic (CT) or magnetic resonance imaging.[8–13] Often, such patients are undergoing abdominal imaging for extra-adrenal cancer diagnosis or screening. Although most isolated adrenal nodules are benign, in patients with a history of malignancy 33% to 75% of adrenal nodules represent metastatic disease.[8,13] In patients with known or suspected extra-adrenal malignancies, FNA cytology plays an important role in differentiating primary adrenal lesions (eg, adrenocortical adenoma) from metastatic cancer.

The management of adrenal nodules depends on the radiographic features, clinical signs and symptoms, and history of malignancy.[8–10] Adrenal lesions are most commonly evaluated by CT scan, as it offers excellent spatial resolution and is available in most clinical settings. Although size criteria are not well established, primary adrenal malignancies and most metastatic disease foci are typically >3 cm. The noncontrast attenuation of the lesion on CT is also important. Adrenal adenomas have high intracellular lipid content, and so attenuation is typically low (<10 HU). Malignant adrenal nodules, whether primary or metastatic, usually display attenuation >10 HU.[11]

The approach taken for FNA depends on the size and location of the lesion and the clinical practice. The adrenal glands can be sampled by FNA with either a percutaneous or endoscopic ultrasound (EUS)-guide approach. Percutaneous FNA of the adrenal glands is typically performed under CT or ultrasound guidance.[14] EUS-guided FNA of adrenal lesions can be performed with a transduodenal approach for the left adrenal and typically a transgastric approach for the right adrenal gland.[14,15] An EUS approach to adrenal gland FNA has the advantage of a low complication rate and nondiagnostic rate compared with a percutaneous approach. However, whereas the left adrenal gland is almost always visible by EUS imaging, the right adrenal gland cannot be identified in up to 70% of patients.[15–17] The right adrenal gland is typically more easily accessed by a percutaneous approach.

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NORMAL ADRENAL ELEMENTS

Normal adrenal and periadrenal elements may be encountered on sampling of adrenal, superior renal, or retroperitoneal lesions. Adrenal cortical cells predominate when non-neoplastic adrenal tissue is aspirated (Fig. 1). Cortical cells may be present in sheets, clusters, or as single cells. Cortical cells have abundant granular or vacuolated cytoplasm, depending on the layer they arise from. Zona glomerulosa and fasciculata cells have lipid-rich, vacuolated cytoplasm, whereas zona reticularis cells have granular cytoplasm that may also contain golden lipofuscin pigment.[1,2] The nuclei are moderately variable in size, but they are typically round with smooth nuclear borders and even chromatin. Adrenal cortical cells are fragile and often rupture on FNA sampling.[2,18] As a result, the background of adrenal smears can resemble adipose tissue due to the presence of lipid-rich vacuoles spilling from the ruptured cortical cell cytoplasm. Naked nuclei are also frequently identified and may cluster.

Noncortical elements are not routinely seen on sampling of adrenal gland tissue. Adrenal medullary cells are located in the center of the gland as organoid nests of cells with abundant granular basophilic cytoplasm and neuroendocrine-type "salt and pepper" chromatin.[1,2] They are not readily identified in adrenal FNA, and the presence of abundant neuroendocrine-type cells should raise the consideration of a neoplastic process such as pheochromocytoma.

FINE NEEDLE ASPIRATION OF ADRENOCORTICAL LESIONS

Adrenocortical lesions include a spectrum of non-neoplastic (adrenal hyperplasia), benign (adrenocortical adenoma), and malignant (adrenocortical carcinoma) processes.[2,18,19] All can show a significant cytomorphologic overlap, and so clinical and radiographic correlation is often necessary for definitive classification. Adrenal hyperplasia is not routinely sampled by FNA. Whereas primary adrenal neoplasms are unilateral and solitary, nodular hyperplasia of the adrenal gland is diffuse and bilateral. Patients with congenital forms of adrenal hyperplasia typically have known clinical history, and laboratory findings (eg, elevation of 17α-hydroxyprogesterone) can confirm the diagnosis.[20]

FNA samples from both adrenocortical adenoma and hyperplastic adrenal nodules are typically moderately cellular, composed of polygonal cells with moderately abundant granular or vacuolar cytoplasm, fine chromatin, and smooth nuclear membranes (Fig. 2).[21] Like normal adrenal cortex, cells are fragile and naked nuclei are often identified. Prominent nucleoli are more commonly seen in adenoma compared to non-neoplastic adrenal cortex.[21] However, in practice, the diagnosis of adenoma generally requires radiographic confirmation of sampling of a solitary adrenal nodule.

The cytologic features of adrenocortical carcinoma are also similar to those seen in adrenal adenomas, and in fact many cases of ACC cannot be distinguished from adrenal adenoma based on cytomorphology alone. Smear slides of ACC show loosely cohesive tumor cells with moderate granular or vacuolated cytoplasm (Fig. 3). Low-grade ACC has cytomorphology similar to adrenocortical adenoma, such as polygonal cells with moderate cytoplasm, fine chromatin, and prominent nucleoli. Radiographic features are typically necessary to differentiate adrenocortical adenoma and low-grade ACC. Solid adrenal lesions that are <4 cm, homogeneous in appearance, and have low noncontrast CT attenuation are typically benign adrenal cortical adenomas. Carcinomas are typically >4 cm, heterogeneous in CT appearance, and often display necrosis.[11] High-grade forms of ACC do display more significant nuclear atypia that may allow for definitive diagnosis of malignancy on FNA. The presence of mitotic activity and necrosis also strongly favors a diagnosis of ACC over adrenal cortical adenoma.[19,21] Intranuclear inclusions are also commonly present in ACC.

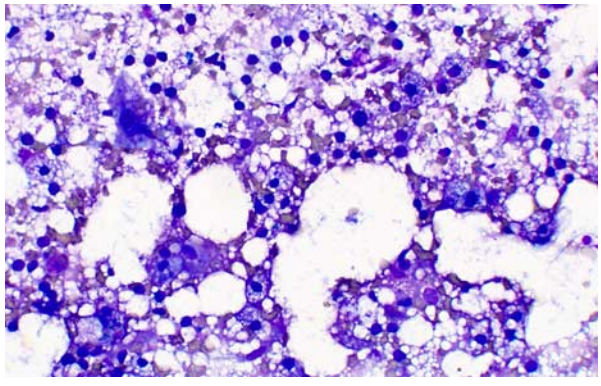

FIGURE 1. Benign adrenal cortical cells. Cells have abundant vacuolated cytoplasm, many of which have ruptured. Lipid vacuoles are abundant within cells and in the background. Cell borders are indistinct (touch preparation, DiffQuik-stained, ×400).

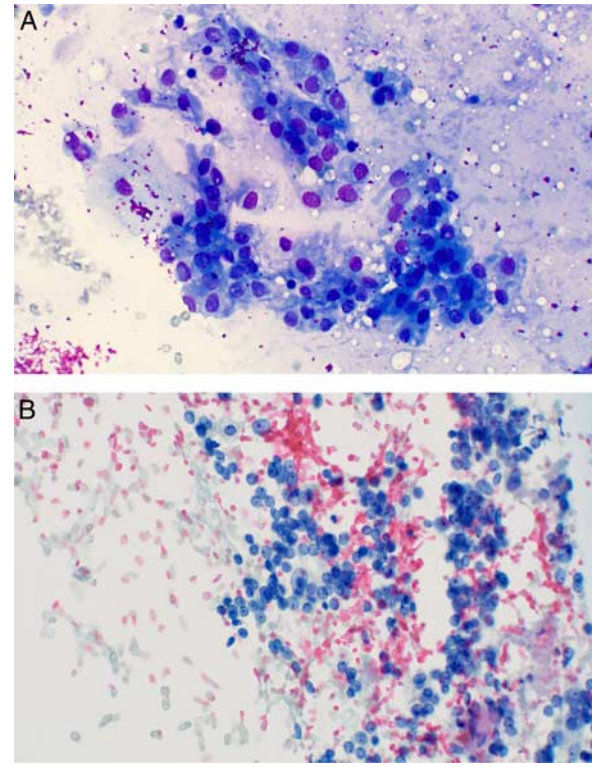

FIGURE 2. Adrenal cortical adenoma. A, Bland adrenal cortical cells with uniform nuclei and moderately abundant cytoplasm. Lipid vacuoles are less prominent than in non-neoplastic adrenal cortex. Naked nuclei are abundant. B, Papanicolaou stained material highlights nucleoli, which are generally absent in non-neoplastic adrenal cortex (conventional smears, DiffQuik-stained and Papanicolaou-stained, ×400). Please see this image in color online.

Adrenal cortical lesions show similar immunohistochemical features regardless of their nature. Steroidogenic factor 1 (SF1), α-inhibin, and Melan A are reliably expressed in all adrenal cortical lesions.[1,22] Synaptophysin is also expressed in adrenal cortical neoplasms, but chromogranin is reliably negative.[22] Ki-67 may be helpful in some cases to differentiate adenoma from ACC, as adenomas have low proliferation (< 5%). ACCs have more variable proliferation, but most cases display Ki-67 indices above 10% at resection.[23] However, the significance of Ki67 proliferative index in cytology specimens has not been well-established.

FINE NEEDLE ASPIRATION OF NONCORTICAL ADRENAL LESIONS

Although most primary neoplasms of the adrenal gland are cortical in origin, occasionally noncortical neoplasms are encountered. Recognition of these rare neoplasms is necessary to avoid misclassification as metastatic disease. The most common of the noncortical neoplasms in adults is pheochromocytoma. Pheochromocytoma is much rarer than adrenal cortical neoplasms, but it is the most common neoplasm arising from the adrenal medulla. Clinical signs and symptoms include hypertension, headache, and elevation of serum or urine catecholamines.[24] When pheochromocytoma is suspected, FNA is contraindicated, as needle trauma can lead to hypertensive crisis due to release of catecholamines into the bloodstream.[25] However, in some cases FNA sampling may occur, especially in patients who are asymptomatic or for whom there is concern for metastatic disease.

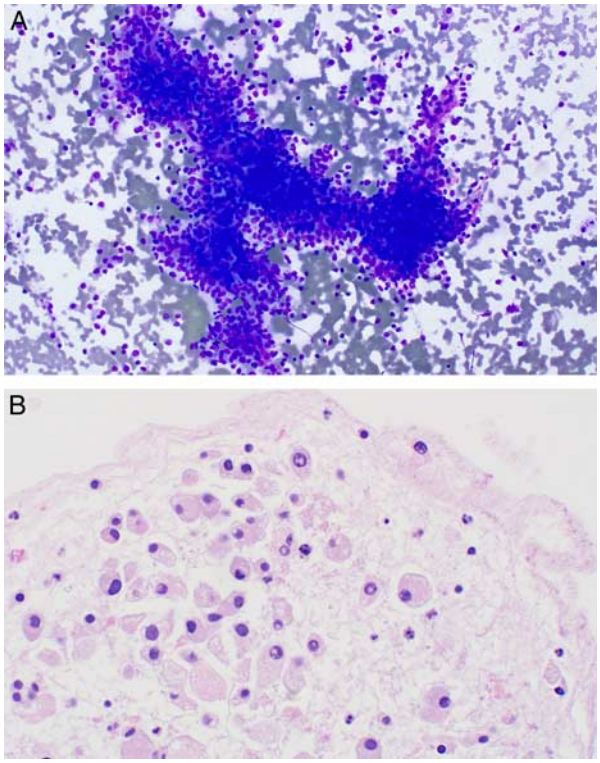

FIGURE 3. Adrenal cortical carcinoma. A, Hypercellular smear composed of loosely cohesive branching groups of tumor cells with traversing capillaries. Cytoplasm is moderately abundant and naked nuclei are noted. B, Cell block demonstrates the lack of cohesion among tumor cells, nuclear pleomorphism, and intranuclear inclusions (conventional smear, DiffQuik stained, ×200 and cell block, hematoxylin and eosin, ×400). Please see this image in color online.

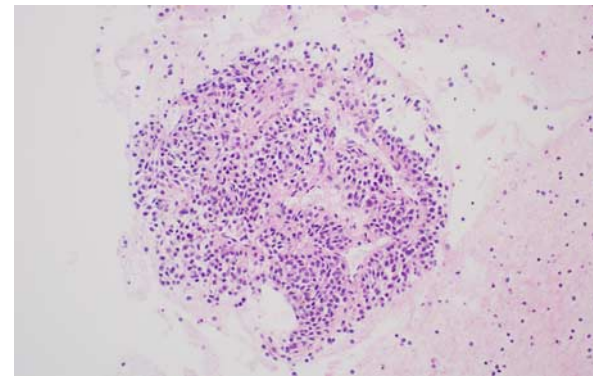

FIGURE 4. Pheochromocytoma. Tumor cells are present in loose, organoid patterns separated by vascular stroma with bland spindle cells. "Salt and pepper" chromatin is noted and nucleoli are absent (cell block, hematoxylin and eosin, ×200). Please see this image in color online.

Pheochromocytomas are variable cellular on FNA sampling, composed of loosely cohesive groups and single cells (Fig. 4). The tumor cells are polygonal to plasmacytoid in appearance, with moderately abundant finely granular cytoplasm.[1,2] Fine salt and pepper chromatin is typical, and intranuclear pseudoinclusions may be seen. Spindle cells (sustentacular cells) may be identified in the background. Immunohistochemical stains for neuroendocrine markers such as synaptophysin and chromogranin are diffusely positive, whereas adrenal cortical markers such as SF1 are negative.[1,22] S-100 highlights sustentacular cells. In contrast to neuroendocrine neoplasms of the lung, pancreas, and other sites, pheochromocytomas lack expression of cytokeratins and epithelial membrane antigen.

Myelolipoma is a rare benign tumor of mixed adipose and hematopoietic elements that occur most commonly in the adrenal gland, typically in middle-aged or older adults. They are asymptomatic, and may come to clinical attention

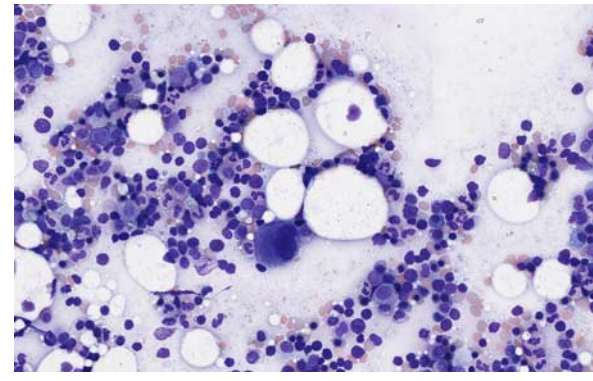

FIGURE 5. Myelolipoma. A mixture of adipose tissue and trilineage hematopoesis is present, including a megakaryocyte in the center of the image (conventional smear, DiffQuik-stained, ×400). Please see this image in color online.

incidentally during abdominal imaging. FNA sampling resembles bone marrow aspirates, with a mixture of adipose tissue and trilineage hematopoietic elements (Fig. 5).[26] They are benign neoplasms and are not associated with the development of hematologic disorders.

Neuroblastoma are malignant, primitive neoplasms of neural crest cells that can occur anywhere along the sympathetic nervous system axis, most commonly within the adrenal gland. They typically occur in children <5 years-old. They may present as large abdominal masses, and urine catecholamines are classically elevated. Morphologically, they seem similar to other "small round blue cell" neoplasms.[1,27] FNA smears are hypercellular, and composed of nested cells with high nuclear-to-cytoplasmic ratios, scant cytoplasm, and finely granular chromatin. Homer Wright rosettes, with acinar arrangements of tumor cells around fibrillary neuropil material, are occasionally identified. Maturation is seen in some cases, in the form of differentiation toward ganglion cells, which seem as single large cells with abundant granular cytoplasm and very large, prominent nucleoli.[27]

METASTATIC MALIGNANCY VERSUS ADRENAL CORTICAL NEOPLASMS

The adrenal gland is a common site of metastatic disease for a wide range of malignancies, including many carcinomas and melanoma.[7] In patients with known or suspected extra-adrenal malignancy, the primary goal of adrenal FNA is to differentiate metastatic malignancy from adrenocortical adenoma. Many metastatic malignancies have cytologic features that overlap with adrenocortical neoplasms, such crowded clusters of cells with moderately abundant granular or vacuolated cytoplasm.[18] However, distinct cytomorphologic and immunohistochemical features can be identified for most metastatic malignancies.

Renal cell carcinoma (RCC) can infiltrate the adrenal gland through metastasis or direct extension.[1] Clear cell RCC is the most common variant and the most frequent form of RCC to metastasize. FNA of metastatic clear cell RCC tends to be hemorrhagic and moderately cellular, with tumor cells present in cohesive clusters of cells with abundant vacuolated or granular cytoplasm (Fig. 6A).[28] Nuclear features vary depending on grade, with fine chromatin and indistinct nucleoli in low-grade RCC and irregular chromatin and nuclear borders and prominent nucleoli in high-grade RCC. Compared with adrenal cortical neoplasms, RCC is more likely to be 3-dimensional in arrangement, contain large glycogen-rich vacuoles, and display erythrophagocytosis.[2,28]

Prostatic adenocarcinoma metastatic to the adrenal gland is present in 13% of patients at autopsy.[29] Tumor cells are typically present in acinar arrangements, composed of tumor cells with moderately abundant granular cytoplasm and prominent nucleoli (Fig. 6B).[28] Naked nuclei and granular background material may be present. The presence of acinar formations and prominent nucleoli favors prostatic adenocarcinoma over adrenal cortical lesions.

Hepatocellular carcinoma (HCC) metastasizes to the adrenal glands in ~10% of cases.[30,31] Metastatic HCC is hypercellular on FNA, composed of tumor cells present in 2-dimensional groups and trabecular arrangements (Fig. 6C). Nuclear-to-cytoplasmic ratios vary, but cytoplasm is typically abundant and prominently granular. Nuclei often display euchromatin, but nucleoli are prominent and intranuclear pseudoinclusions can be identified. Like adrenal cortical carcinoma, traversing capillaries can be seen associated with tumor cells. In contrast to adrenal cortical neoplasms, cell borders tend to be well defined and

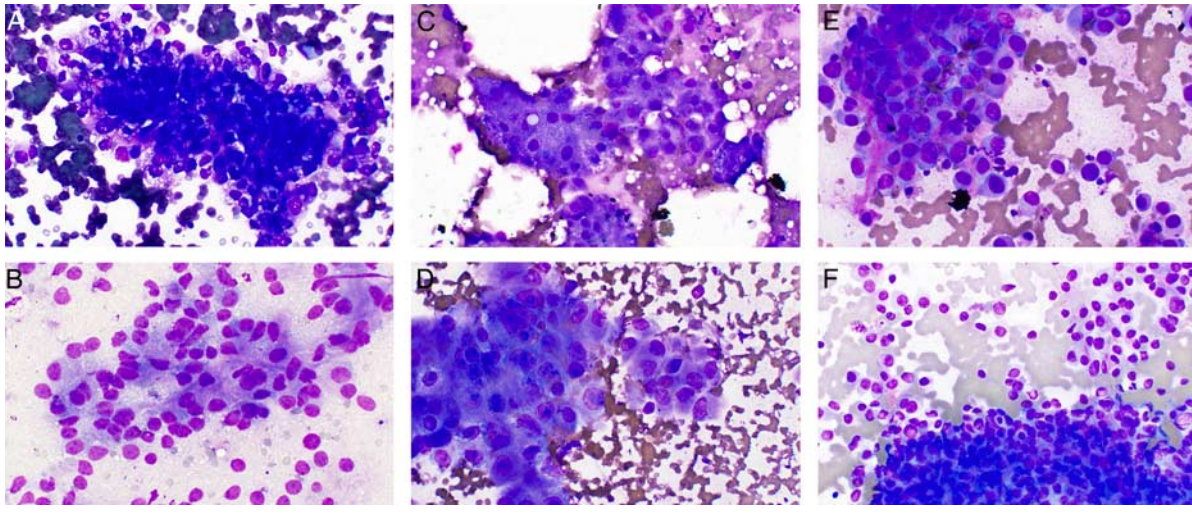

FIGURE 6. Carcinomas of various sites can involve the adrenal gland. Renal cell carcinoma (A) exhibits tumor cells in 3-dimensional clusters, composed of large cells with clear cytoplasm but lacking the lipid-rich background of adrenal cortex. Prostatic adenocarcinoma (B) like adrenal cortex is composed of cells with granular or vacuolated cytoplasm, but acinar arrangements and prominent nucleoli help identify its origin. Lung adenocarcinoma (C) also displays cells with abundant cytoplasm that may be vacuolated, but significant nuclear atypia and prominent nucleoli are typical for metastatic disease. Hepatocellular carcinoma (D) also contains granular cytoplasm and may have lipid vacuoles, but shows a greater cohesion than adrenal cortical neoplasms and intracytoplasmic pigment, such as the blueish iron granules at the bottom of the image. Melanoma (E) can show loosely cohesive cells with granular cytoplasm, but eccentric nuclei and prominent nucleoli suggest the diagnosis. Adrenal cortical carcinoma (F) exhibiting cytologic atypia and morphologically overlapping with metastatic carcinomas. Immunohistochemistry for SF1 can confirm the diagnosis of adrenal cortical carcinoma (conventional smears, DiffQuik-stained, ×400).

pseudoacinar arrangements are commonly present. Intracytoplasmic iron pigment, bile plugs, and hyaline globules may also be seen.

Adenocarcinomas from multiple organ sites, especially lung and breast, also commonly metastasize to the adrenal glands.[5–7,28] Like adrenal cortical neoplasms, they may display cells with abundant granular or vacuolated cytoplasm. Most metastatic adenocarcinomas have overt malignant features on aspiration, such as marked nuclear pleomorphism and anisonucleosis (Fig. 6D). When present, 3-dimension groups and glandular formations assist in the diagnosis of metastatic adenocarcinoma to the adrenal gland.

Melanoma is the most common nonepithelial solid malignancy to metastasize to the adrenal glands.[7,18] Like adrenal cortical carcinoma, they often present on FNA as loosely clustered groups of tumor cells with numerous single tumor cells (Fig. 6E). Moderately abundant and occasionally granular cytoplasm is seen. Cell borders are more distinct than in adrenal cortical neoplasms, and eccentric nuclei with prominent nucleoli are characteristic.

THE ROLE OF IMMUNOHISTOCHEMISTRY IN ADRENAL GLAND CYTOLOGY

The primary role of immunohistochemistry in adrenal FNA cytology is to differentiate adrenal cortical lesions from metastatic disease, and in the latter case to confirm the site of origin. Although extra-adrenal malignancies have significant cytomorphologic overlap with adrenal cortical neoplasms, the immunohistochemical features of these tumors generally allows for primary classification (Table 1). Adrenocortical neoplasms, including both adenomas and carcinomas, express unique markers not routinely seen in other epithelial neoplasms. SF1 is a highly sensitive and specific marker of adrenal cortical neoplasms in most settings, as SF1 expression is almost never seen in extra-adrenal epithelial or melanocytic lesions.[32] Inhibin and Melan A expression also assist in the diagnosis.

Cytokeratin 7 is expressed in most forms of adenocarcinoma, including lung and breast carcinomas. However, adrenocortical neoplasms are negative for cytokeratin 7, and a number of other metastatic malignancies that commonly metastasize to the adrenals lack cytokeratin 7 expression, including RCC, PCA, and HCC.[33] Fortunately, a panel of SF1 (ACC), PAX8 (RCC), NKX3.1 (PCA), and Glypican 3 (HCC) can differentiate the common cytokeratin 7 negative malignancies that involve the adrenal gland.[33,34] Likewise, melanoma is cytokeratin negative, but expression of melanocytic markers such as SOX10 and HMB45 can confirm the diagnosis. Notably, however, Melan A is expressed in both melanoma and adrenocortical neoplasms.

Occasionally, neuroendocrine neoplasms of the lung, pancreas, or other sites can metastasize to the adrenal gland. When metastasis of neuroendocrine tumors is suspected, pheochromocytoma must be ruled out. Although both show similar cytomorphologic features, including nests and trabeculae of tumor cells with fine chromatin, pheochromocytomas lack cytokeratin expression.[35] In contrast, metastatic neuroendocrine tumors metastatic to the adrenal gland retain cytokeratin expression.

PROPOSED CLASSIFICATION SYSTEMS FOR ADRENAL GLAND CYTOLOGY

In the past few decades, there has been ongoing effort to standardize reporting systems for cytology specimens. The first Bethesda System for Reporting Cervical Cytology was introduced in 1988, with updated revised editions in 2001 and 2014. In more recent years, classification and reporting systems have been developed for FNA cytology at a number of sites, including the Bethesda System for Reporting Thyroid Cytopathology (2010), the Papanicolaou Society of Cytopathology System for Reporting Pancreaticobiliary Cytology (2015), and the Milan System for Reporting Salivary Gland Cytopathology (2015), and Guidelines of The Papanicolaou Society of Cytopathology System for Reporting Respiratory Cytology (2016).[36] To date, there has not been widespread acceptance of a reporting system for adrenal gland FNA cytology. However, recently 2 possible systems have been proposed.

In 2020, Mustafa et al[37] proposed a 7-tier diagnostic classification system for adrenal lesions based on their retrospective analysis of 484 cases within a single institution. Their proposed system uses identical categories to the Milan System for Reporting Salivary Gland Cytopathology, including indeterminate categories of 3 [atypia of undetermined significance (AUS)], 4a (neoplastic, benign), and 4b (neoplastic, uncertain malignant potential [UMP]) (Table 2). Category 3 (AUS) is reserved for cases with cytologic atypia but lacking definitive evidence of a neoplastic process. Category 4a (neoplastic, benign) includes cases with cytologic and radiographic findings consistent

TABLE 1. Immunohistochemical Stain Expression in the Differential Diagnosis of Adrenal Gland Malignancies

	SF1	Inhibin	Cytokeratin 7	TTF-1	GATA-3	PAX-8	NKX3.1	Glypican 3	SOX10
Adrenal cortical carcinoma	Positive	Positive	Negative	Negative	Negative	Negative	Negative	Negative/positive*	Negative
Lung, adenocarcinoma	Negative	Negative	Positive	Positive	Negative	Negative	Negative	Negative	Negative
Breast, ductal carcinoma	Negative	Negative	Positive	Negative	Positive	Negative	Negative	Negative/positive*	Positive/negative†
Kidney, renal cell carcinoma, clear cell type	Negative	Negative	Negative	Negative	Negative	Positive	Negative	Negative	Negative
Prostate, adenocarcinoma	Negative	Negative	Negative	Negative	Negative	Negative	Positive	Negative	Negative
Liver, hepatocellular carcinoma	Negative	Negative‡	Negative	Negative	Negative	Negative	Negative	Positive	Negative
Melanoma	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Positive

*Hepatoid adenocarcinomas of the lung and a minority of breast carcinomas express glypican 3.
†SOX10 expression is identified in many "triple-negative" breast cancers.
‡Inhibin expression has been described in rare cases of hepatocellular carcinoma.
SF1 indicates steroidogenic factor 1.

TABLE 2. Proposed Adrenal Gland Fine Needle Aspiration Classification Systems With Implied Rates of Malignancy

Mustafa et al[37] Classification System		Trabzonlu et al[38] Classification System	
Category	**Rate of Malignancy n (%)***	**Category**	**Rate of Malignancy n (%)***
I. Nondiagnostic	NA	I. Unsatisfactory	10/35 (30)
II. Non-neoplastic	1/16 (6)	II. Non-neoplastic	0/1 (0)
III. Atypia of undetermined signifiance	2/4 (50)	III. BACE	0/21 (0)
IVa. Neoplastic-benign	0/4 (0)	IV. NONC	0/6 (0)
IVb. Neoplastic–uncertain malignant potential	2/4 (50)	V. Atypia of undetermined significance	10/21 (48)
V. Suspicious for malignancy	3/4 (75)	VI. Suspicious for malignancy	6/6 (100)
VI. Malignant	36/36 (100)	VII. Malignant	87/88 (98.9)

*Rate of malignancy calculated based on cases with concurrent or follow-up surgical pathology diagnosis.
BACE indicates bland appearing adrenal cortical cells; NA, not applicable; NONC, noncortical neoplasm.

with adrenocortical adenoma. Category 4b (neoplastic, UMP) includes cases consistent with pheochromocytoma or with indeterminate features between adrenal cortical adenoma and carcinoma. No malignancy was identified on follow-up in patients classified as neoplastic-benign (0/4), whereas AUS (2/4) and neoplastic-UMP (2/4) cases were malignant on follow-up in 50% of cases.

In 2022, Trabzonlu and colleagues proposed a novel classification system for adrenal gland cytology based on retrospective analysis of 473 cases across multiple institutions (Table 2). Their recommended adrenal gland FNA classification system is also 7-tiered. However, the indeterminate categories they suggest take into account cell lineage. Category 3 (benign adrenal cortical elements [BACE]) is reserved for cases composed of benign adrenal cortical cells lacking atypia, and encompasses non-neoplastic and benign neoplastic adrenal cortical lesions. Category 4 (primary neoplasm of noncortical origin [NONC]) includes low-grade lesions of medullary origin, such as pheochromocytoma and ganglioneuroma. Category 5 (AUS) includes cases with cytologic atypia but lacking definitive diagnostic features, often due to low cellularity. No malignancy was identified in cases classified as BACE (0/21) or NONC (0/6), but AUS cases were malignant on follow-up in 48% (10/21) of cases.

It remains to be seen whether a standardized system will be widely accepted for adrenal gland FNA cytology. However, these proposed classification systems and their follow-up data suggest that the presence of cytologic atypia in FNA sampling should always be reported, as even indeterminate atypia (AUS) classification indicated malignancy in 48% of cases (12/25) across the 2 studies and 50% (2/4) of cases classified as "neoplastic-UMP" from Mustafa and colleagues. Notably, in both studies the finding of adrenal cortical cells without significant atypia was reassuring for benign classification, as malignancy was found in 0% of cases classified as benign-neoplastic or BACE (0/25).

CONCLUSION

FNA of the adrenal gland remains an important diagnostic tool in the workup of patients with known or suspected malignancy. Lesions >4 cm in dimension or with suspicious features on abdominal imaging are typically malignant, but smaller adrenal nodules may harbor benign or malignant neoplasms. Although most small adrenal nodules are benign, metastatic disease must be ruled out in patients with a history of extra-adrenal malignancy. Although there is morphologic overlap between adrenal cortical lesions and metastatic carcinomas, careful examination of cytomorphologic features and ancillary immunohistochemistry can differentiate adrenal cortical neoplasms from the various metastatic malignancies that involve the adrenal gland. A panel of SF1, cytokeratin 7, and other organ specific markers (Table 1) are helpful in most cases. Biopsy of pheochromocytoma is typically contraindicated, but when sampled the combination of neuroendocrine cytomorphologic features and absent cytokeratin expression can establish the diagnosis. Although there is no widely agreed upon classification system for FNA diagnosis of adrenal gland neoplasms, cytology reports of primary adrenal neoplasms should state the nature of the lesion [adrenal cortical vs. noncortical (eg, pheochromocytoma, myelolipoma)] and the presence or absence of cytologic atypia.

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