

## CYTOLOGY OF ADRENAL LESIONS

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### ABSTRACT

Cystic and solid lesions in the adrenal glands commonly present as mass lesions and have varied etiology as infectious diseases, benign cysts, adrenal neoplastic lesions and metastasis. Smaller sized and nonfunctional small adrenal lesions, incidentaloma, are being picked up with the advancement in the radiological diagnostic modalities and widespread use of CT scans and USG. Main use of the FNA of adrenal lesions is to ascertain origin and character of cystic and solid adrenal masses, distinguishing benign adrenal nodules from metastatic tumors and diagnosis of infectious diseases commonly presenting as adrenal insufficiency (disseminated histoplasmosis). Radiological guided FNAC of adrenal gland provides an easy and quick method for the diagnosis of these lesions.

**Key Words :** Adrenal gland, Mass lesions, Guided FNAC, Cytology.

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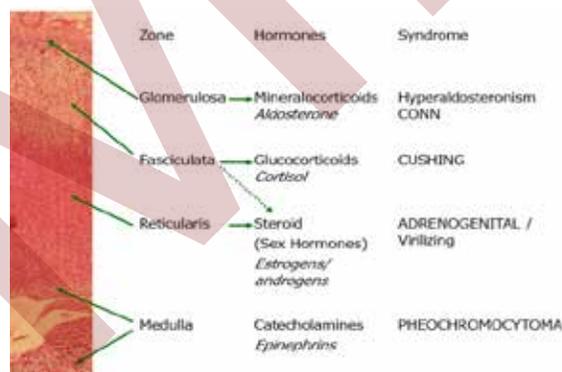
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### INTRODUCTION

A working knowledge of the pathophysiology of the gland and familiarity with the clinical and laboratory data are important while dealing with FNAC of adrenal lesions and examining the gross and microscopic features of the biopsied or resected adrenal gland. Vastly different pathophysiologic mechanisms may lead to the same clinical syndromes. With the advancement of imaging modalities and smaller size of sampled adrenal gland (core needle biopsies/ guided FNAC) and picking up and resection of non-functional incidentalomas, poses additional diagnostic challenges to the pathologist. (1)

### BRIEF ANATOMY

The adrenal glands are paired endocrine organs consisting of both cortex and medulla, which differ in their development, structure, and function. In the normal adult each adrenal gland measures approximately 5 × 3 × 1 cm. Left gland is crescentic and right gland is pyramidal in shape in adults. Normal weight in adults is 4-6 grams each after dissection of fat, acute stress reduces lipid content and weight, prolonged stress induces hypertrophy and hyperplasia and increases weight. Adrenal gland has a complete fibrous capsule, which may merge with capsule of kidney (either gland), and liver (right sided gland). Beneath the capsule of the adrenal is the narrow layer of zona glomerulosa (ZG). An equally narrow zona reticularis (ZR) abuts the medulla. Intervening is the broad zona fasciculata (ZF), which makes up about 75% of the total cortex. Cortex is bright yellow due to lipid. ZG is composed of small angular cells with a high nuclear to cytoplasmic ratio, ZF with large clear lipid laden cells arranged in columns and ZR comprises eosinophilic (compact) cells with little lipid storage arranged in cord around vascular sinusoids. Medulla has ellipsoid



**Figure 1.** Part of adrenal gland and corresponding hormones and related syndromes

shape and is gray-tan and <10% of gland volume (1% in neonates) and is more prominent with cortical atrophy. (2)

Laboratory evaluation of adrenocortical function: Blood Levels:

Peptides: The plasma levels of ACTH, angiotensin II, *Plasma Corticotropin-Releasing Hormone*

Steroids: Cortisol and aldosterone are both secreted episodically. Measurement of the sulfate conjugate of DHEA may be a useful index of adrenal androgen secretion. (3)

Urine Levels: Measurement of urinary free cortisol  
Stimulation Tests: are useful in the diagnosis of hormone deficiency (adrenal insufficiency) states.

**Tests of Glucocorticoid Reserve:** Within minutes after administration of ACTH, cortisol levels increases. This responsiveness can be used as an index of the functional reserve of the adrenal gland for production of cortisol. (4)

**Tests of Mineralocorticoid Reserve and Stimulation of the Renin-Angiotensin System:** When the dietary sodium intake is normal, stimulation testing requires the administration of a potent diuretic, such as 40–80 mg furosemide, followed by 2–3h of upright posture. The normal response is a two- to fourfold rise in plasma aldosterone levels. (11, 12, 14)

**Suppression Tests:** Suppression tests to document hypersecretion of adrenal hormones, involve measurement of the target hormone response after standardized suppression of its tropic hormone. (13, 17, 18)

**Indications of FNA in adrenal lesion:** Main use of FNA of adrenal lesions is to ascertain origin and character of cystic & solid adrenal masses, distinguishing benign adrenal nodules from metastatic tumors (the adrenal gland is a common site of metastasis from tumors elsewhere in the body) and diagnosis of infectious diseases commonly presenting as adrenal insufficiency (disseminated histoplasmosis). With widespread use of CT scans & USG, many smaller lesions of adrenal (incidentalomas) are being picked up and subjected to guided FNA/ trucut biopsies. (14, 18)

**Procedure & usefulness of FNA in adrenal lesions:** FNA of adrenal gland is done under imaging (CT/US guided) by either percutaneously or by Direct/ transhepatic approach. Relatively safe procedure and complications include mild-minimal hematuria, self-limited hypotension and bradycardia. Rare serious complications include pneumothorax and hemothorax. FNA smears of adrenal should be very gently smeared because adrenal cortical cells have extremely fragile cytoplasm. Guided FNA smears are dry and wet fixed and stained with MGG, Papanicolaou & H & E stains. Cell blocks may be prepared to perform immunohistochemistry, which is at times crucial in differentiating adrenocortical lesions with metastasis in adrenal gland. (15, 17)

FNA in adrenal lesions has an accuracy of around 97%, and good negative predictive value, particularly for lesions larger than 3 cm. False-positive results are uncommon. Rarely, the cells of a benign adrenal nodule or adenoma may be misinterpreted as metastatic small cell carcinoma. The non diagnostic rate is around 14%. (16)

### ADRENAL INCIDENTALOMA:

Advancements in medical imaging have led to the incidental discovery of non-functional adrenal masses of varying sizes (incidentalomas) in asymptomatic individuals (or in individuals in whom the presenting complaint is not directly related to the adrenal gland. Incidence is approximately 4%. They are usually detected after 35 years of age. *The vast majority of adrenal incidentalomas are small non-secreting cortical adenomas of no clinical importance.* (17)

#### Adrenal lesions:

- Adrenocortical hyperplasia, nodular hyperplasia
- Adrenal cortical adenomas, Conn's adenoma
- Adrenocortical carcinoma
- Pheochromocytoma (intra-adrenal paraganglioma)

- Neuroblastoma
- Ganglioneuroma
- Ganglioneuroblastoma (malignant ganglioneuroma)
- Adrenal Lymphoma
- Metastasis in adrenal gland
- Adrenal cysts
- Adrenal myelolipoma
- Adrenal infection

**Adrenocortical benign lesions (adenoma/nodular hyperplasia):** Adrenal hyperplasia and adenoma or indistinguishable on cytology. Cytomorphology of benign adrenal cortical nodule or adenoma reveals numerous naked nuclei on a “frothy”, granular background and occasional intact cells with indistinct cell border and bubbly cytoplasm. (18)

**Adrenocortical carcinoma:** Differentiation from adrenocortical adenoma and adrenocortical denmoma requires Weiss criteria on histology. Cytomorphological features which indicates adrenocortical carcinoma are numerous isolated cell with intact cytoplasm, presence of moderate to marked nuclear atypia, mitosis, atypical mitosis and necrotic debris. To differentiate adrenocortical carcinoma from renal cell carcinoma, pheochromocytoma and metsasis, use of immunocytochemistry is very important. (Table 1). (14).

**Table 1 :** Immunostains in adrenal lesions:

### PHEOCHROMOCYTOMA (INTRA-ADRENAL PARAGANGLIOMAS):

A presumptive diagnosis of pheochromocytoma is based on the combination of an adrenal mass, hypertension, and elevated blood and urinary levels of catecholamines. Cytologic preparations are highly cellular and contain cells arranged in loose clusters and as isolated cells. Cellular pleomorphism can be marked, with small polygonal cells admixed with large spindle-shaped cells with abundant fibrillary cytoplasm. Nuclei are pleomorphic and irregular in contour. The chromatin is finely stippled; intranuclear cytoplasmic pseudoinclusions and prominent nucleoli may be present. Red cytoplasmic granules may be present on MGG stain. With alcohol-fixed, Pap-stained preparations, the cytoplasm has a characteristic, deep red-to-purple, granular appearance. Pheochromocytoma can resemble an adrenal cortical neoplasm. Immunostains help in differentiating these lesions (Table 1). (20)

### ADRENAL MYEOLIPOMA:

Adrenal myelolipoma are uncommon benign neoplasm and composed of adipose tissue and benign hematopoietic elements. FNA smears show fat with interspersed marrow elements including nucleated red blood cells, megakaryocytes, and granulocytes and their precursors (all three lineages). Differential diagnosis includes angiomyolipoma of the kidney which is distinguished by presence of hematopoietic elements and absence of smooth muscle cells and negative HMB45 immunostain. (21)

**METASTATIC TUMORS IN ADRENAL GLAND:**

FNA of the adrenal gland is useful to confirm or rule out an adrenal metastasis in a patient with a history of cancer and also in distinguishing metastatic tumor nodules with benign adrenocortical conditions. The most common metastases encountered by FNA are from lung cancers, melanoma, and

RCC. Metastatic adenocarcinomas from the lung, kidney, breast, and other sites can look like an adrenal cortical carcinoma. Immunostains are helpful in distinguishing adrenocortical lesions from metastasis eg; TTF-1 for metastatic adenocarcinoma or small cell carcinoma of the Lung, S-100 and HMB-45 for melanoma (Table 1). (5, 6)

**Table 1 : Immunostains in adrenal lesions:**

	Adrenocortical Ca /adenoma hyperplasia	Pheochrome-cytoma	Renal Cell carcinoma	Metastasis
Vimentin	+	-	+	+/-
CK	-	-	+	+/-
EMA	-	-	+	+/-
Chromogranin	-	+	-	+/-
Inhibin	+	-	-	-
A103/Melan A	+	-	-	-
Calretinin	+	-	-	-

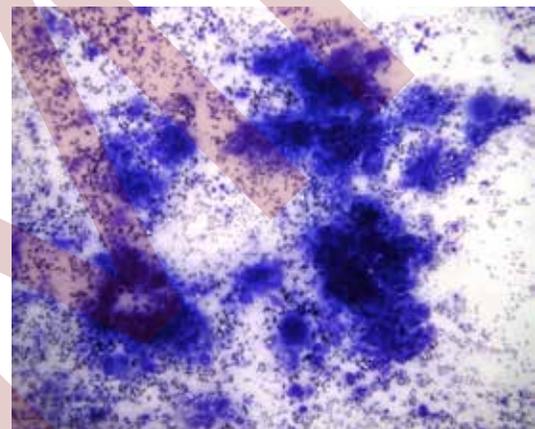
**Adrenal infections:** are usually part of systemic disease and any infection can occur in the adrenal glands. (7)

**Tuberculosis** accounts for approx 70% of Addison's disease in developing countries. On FNA tuberculosis of adrenal show extensive caseating necrosis and poorly formed granulomatous response. (8)

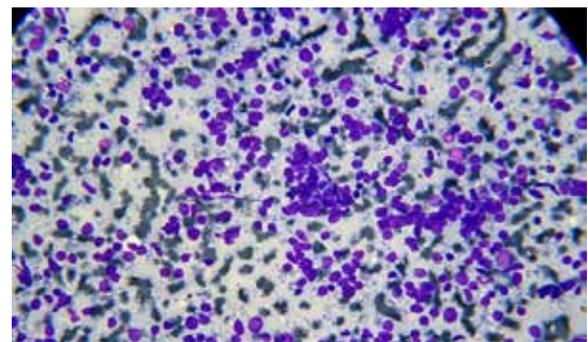
**Fungal infections** of adrenal are discovered in working up a PUO or adrenal cortical insufficiency. Adrenal insufficiency usually occurs when >90% of the adrenal is destroyed. fungal infections of adrenal include histoplasmosis, blastomycosis, coccidiomycosis and cryptococcosis. Commonest fungal infection of adrenal is histoplasmosis. Disseminated histoplasmosis presents as bilateral adrenal mass and may present as adrenal insufficiency. On cytomorphology histoplasmosis show caseating necrosis, blunted granulomatous response and organisms may aggregate in macrophages. Characteristic features of histoplasma are tiny 2- to 4-µm oval yeasts that reproduce by budding and parasitize macrophages. Awareness of histoplasmosis and early diagnosis with FNA is important as timely antifungal treatment (amphotericin B) prevents mortality and morbidity (Table 2). (9, 10)

**Table 2 : Adrenal histoplasmosis at SGPGI Experience**

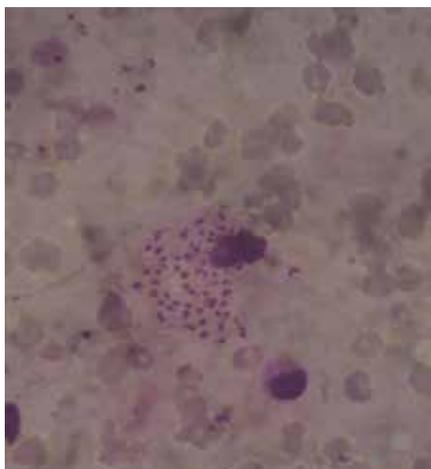
Period	(2006-2009)
M:F	8:0
Age	Median 55 yrs ; range (45-66 years)
Fever, Wt Loss	All cases
Bilateral adrenal enlargement	8/8
Adrenal Insufficiency	3/8
Diagnosis	Guided FNA 6/8, Histology 2/8
Treatment:	Amphotericin B-2weeks, followed by Itraconazole- 1year.



**Figure 2.** Guided FNA smear from adrenal showing large atypical polygonal cells from case of adrenal cortical carcinoma. (MGG X100 original magnification)



**Figure 3.** Guided FNA smear from adrenal showing large atypical polygonal cells from case of adrenal lymphoma. (MGG X100 original magnification)



**Figure. 4.** Guided FNA smear from a case of adrenal insufficiency showing tiny oval budding yeasts inside and outside macrophage (H&E X1000 original magnification)

## CONCLUSION

A proper clinical workup and correlation with laboratory parameters and radiological findings are essential in interpretation of FNA in adrenal lesions. Guided FNAC in adrenal lesions helps in differentiating adrenal neoplasm from metastasis in adrenal gland. Common infections in the adrenal gland include adrenal Histoplasmosis and adrenal tuberculosis. FNA plays major role in early diagnosis of adrenal infections.

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