King Saud University
College of Medicine
Second year – Endocrine Block

Pathology of the Adrenal Glands

Lecture - 3

430 Pathology Team

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Red: Doctors' and important notes.
Green: Team notes.

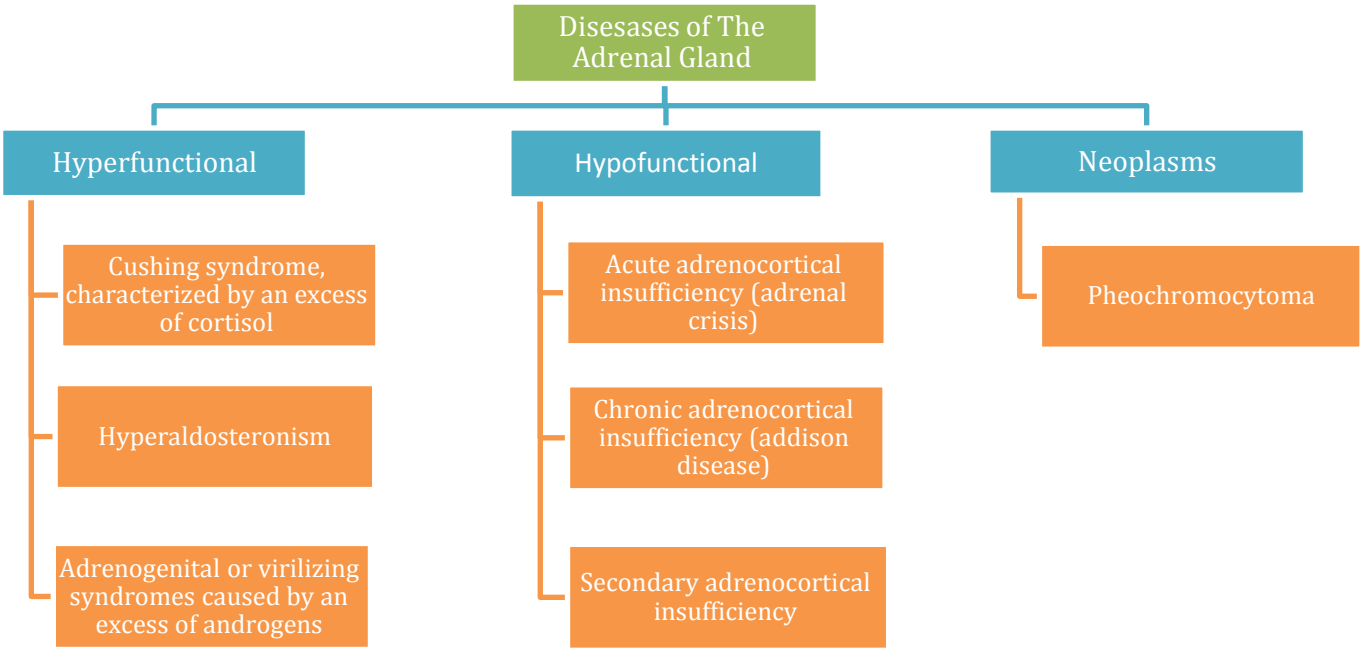
Adrenal Glands:

Anatomy:

The adrenal glands are paired endocrine organs consisting of

1. cortex with its three layers:
    - Zona glomerulosa (secretes mineralocorticoids mainly aldosterone)
    - broad zona fasciculata (75%) of the total cortex (secrets glucocorticoids principally cortisol)
    - Zona reticularis (secrets sex steroids such as estrogens and androgens).
2. Medulla which is composed of chromaffin cells which synthesis and secret catecholamines, mainly epinephrine.

Pathology:



1. Cushing syndrome: is a disorder caused by any condition that produces an elevation in glucocorticoid levels.

- Broadly divided into *exogenous* and *endogenous* causes.
- *The vast majority of cases of Cushing syndrome are the result of the administration of exogenous glucocorticoids* ("iatrogenic" Cushing syndrome).
- The endogenous causes can, in turn, be divided into those that are *ACTH dependent* and those that are *ACTH independent*

The morphology of the **adrenal glands** depends on the cause of the hypercortisolism.

The adrenals can have one of the following abnormalities:

(1) **Cortical atrophy: results from exogenous glucocorticoids.** This atrophy happens due to a lack of stimulation of the zonae fasciculata and reticularis by ACTH. The zona glomerulosa is of normal thickness in such cases, because this portion of the cortex functions independently of ACTH.

(2) **Diffuse hyperplasia: individuals with ACTH-dependent Cushing syndrome.**

(3) **Macronodular (less than 3cm), or micronodular(1-3mm) hyperplasia**

(4) **Adenoma or carcinoma**

Cause	Relative Frequency (%)	Ratio of Females to Males
ACTH-DEPENDENT		
Cushing disease (pituitary adenoma; rarely CRH-dependent pituitary hyperplasia)	70	3.5:1.0
Ectopic corticotropin syndrome (ACTH-secreting pulmonary small-cell carcinoma, bronchial carcinoid)	10	1:1
ACTH-INDEPENDENT		
Adrenal adenoma	10	4:1
Adrenal carcinoma	5	1:1
Macronodular hyperplasia	<2	1:1
Primary pigmented nodular adrenal disease	<2	1:1
McCune-Albright syndrome	<2	1:1

Clinical features Of Cushing's	% Of Occurrence
Obesity or weight gain	95%[*]
Facial plethora	90%
Rounded face	90%
Decreased libido	90%
Thin skin	85%
Decrease in linear growth in children	70–80%
Menstrual irregularity	80%
Hypertension	75%
Hirsutism	75%
Depression/emotional liability	70%
Easy bruising	65%
Glucose intolerance	60%
Weakness	60%
Osteopenia or fracture	50%
Nephrolithiasis	50%

Adrenocortical hyperplasia. The adrenal cortex (bottom) is yellow, thickened, and multinodular as a result of hypertrophy and hyperplasia of the lipid-rich zonae fasciculata and reticularis. The top shows a normal adrenal for comparison.

2. Hyperaldosteronism:

Definition: excess aldosterone secretion that results in Sodium retention and potassium excretion with resultant hypertention and hypokalemia.

Note: Aldosterone causes potassium secretion into urine. With high levels of aldosterone, hypokalemia develops and can be severe enough to cause Neuromuscular problems like muscle weakness, paresthesias, and even tetany

- Primary hyperaldosteronism may be the most common cause of secondary hypertension (i.e., hypertension secondary to an identifiable cause).

- Has an estimated prevalence rate of 5% to 10% among nonselected hypertensive patients.

- Although aldosterone-producing adenomas account for less than 1% of cases of hypertension, it is important to recognize them, because they cause a surgically correctable form of hypertension.

Types:

1. Primary Hyperldosternosum: (autonomous overproduction of aldosterone)
   This excess production results in the suppression of the renin-angiotensin system and decreased renin plasma level.

This overproduction is usually caused by:

A. An aldosterone producing adrenocortical neoplasms usually adenoma such as Conn syndrome
B. Primary adrenocortical hyperplasia of the.(discussed later)

Note: there is a lot of debate about what is the most common cause primary Hyperldosternosum, but the two previous causes are by far the most common.

2. Secondary Hyperldosternosum:

- The aldosterone release is in response to the activation of the renin-angiotensin system.
- The plasma level of renin is high.

This can be seen in:

1) Decreased renal perfusion (arteriolar nephrosclerosis, renal artery stenosis)
2) Arterial hypovolemia and edema (congestive heart failure, cirrhosis, nephrotic syndrome)
3) Pregnancy (due to estrogen-induced increases in plasma renin substrate).

A. Primary adrenocortical hyperplasia (idiopathic hyperaldosteronism):

Characterized by: bilateral nodular hyperplasia of the Zona glomerulosa.

Glucocorticoid-remediable hyperaldosteronism is another, but rare cause of hyperaldosteronism (GRA) is a hereditary form of primary hyperaldosteronism that presents with hypokalemia and hypertension from childhood onward. The activation of aldosterone secretion is under the influence of ACTH and hence is suppressible by exogenous administration of dexamethasone.

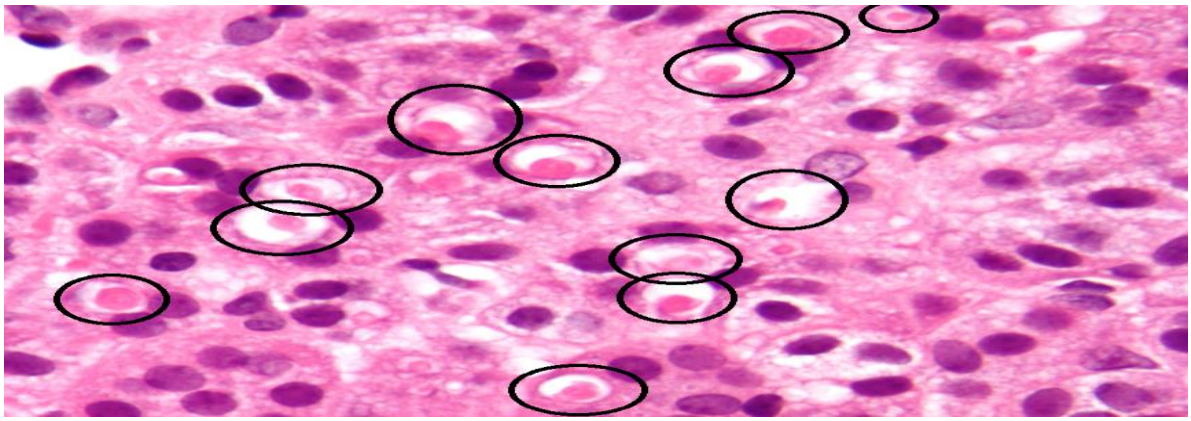
B. Conn's Syndrome: is an aldosterone-producing adenoma.

Incidence of Conn's Syndrome:

- Occurs to people in their thirties and forties
- women more often than in men

Morphology of an aldosterone secreting adenoma: (important)

1. Solitary
2. small (<2 cm in diameter)
3. well-circumscribed lesions (encapsulated)
4. Occurs in left gland > right one
5. buried within the gland and do not produce visible enlargement
6. bright yellow on cut section surprisingly, they are composed of lipid- laden cortical cells more closely resembling fasciculata cells than glomerulosa cells (the normal source of aldosterone)
7. The cells tend to be uniform in size and shape(mature cortical cells)
8. The characteristic feature is the presence of eosinophilic, laminated cytoplasmic inclusions, known as spironolactone bodies. These are typically found after treatment with spironolactone (antihypertensive)



Histological features of an adrenal cortical adenoma: The neoplastic cells are vacuolated because of the presence of intracytoplasmic lipid. There is a mild nuclear pleomorphism.

3. Adrenal Insufficiency:

It is also known as hypofunction, may be caused by either primary adrenal diseases (primary hypoadrenalism) or decreased stimulation of the adrenal resulting from deficiency of ACTH (secondary hypoadrenalism).

Patterns of adrenocortical insufficiency can be:

1. Acute adrenocortical insufficiency (adrenal crisis)
2. Primary chronic adrenocortical insufficiency (Addison disease)
3. Secondary adrenocortical insufficiency happens due to decreased ACTH secretion like those seen in pituitary or hypothalamic diseases. Another cause of secondary adrenal insufficiency is prolonged exogenous glucocorticoids that suppress the HPA and cause the insufficiency upon withdrawal. One of the differences between primary and secondary is lack of pigmentation in secondary because there is decreased ACTH secretion.

Causes:

Acute (may present as a shock)
- Acute hemorrhagic necrosis (Waterhouse-Friderichsen syndrome) associated with Neisseria meningitis sepsis. - Drug- and steroid-induced inhibition of adrenocorticotropic hormone or cortical

Chronic
Major contributor: - Isolated autoimmune adrenalitis (polygenic) (most common) - Tuberculosis - Acquired immune deficiency syndrome (AIDS) - Metastatic carcinoma
Minor contributor: - Amyloidosis, sarcoidosis, hemochromatosis (infiltrative diseases) - Fungal infection

Other causes:

- Loss of cortex
- Autoimmune polyendocrinopathy syndrome type 1 (*AIRE-1 gene on 21q22)*
- Autoimmune adrenal insufficiency Congential adrenal hypoplasia
- X-linked adrenal hypoplasia (DAX-1 gene on Xp21)
- "Miniature" type adrenal hypoplasia (unknown cause)
- Adrenoleukodystrophy (ALD gene on Xq28)
- Autoimmune polyendocrinopathy syndrome type 2 (polygenic)
- Metabolic failure in hormone production
- Congenital adrenal hyperplasia (cortisol and aldosterone deficiency with virlization)

Addison Disease:

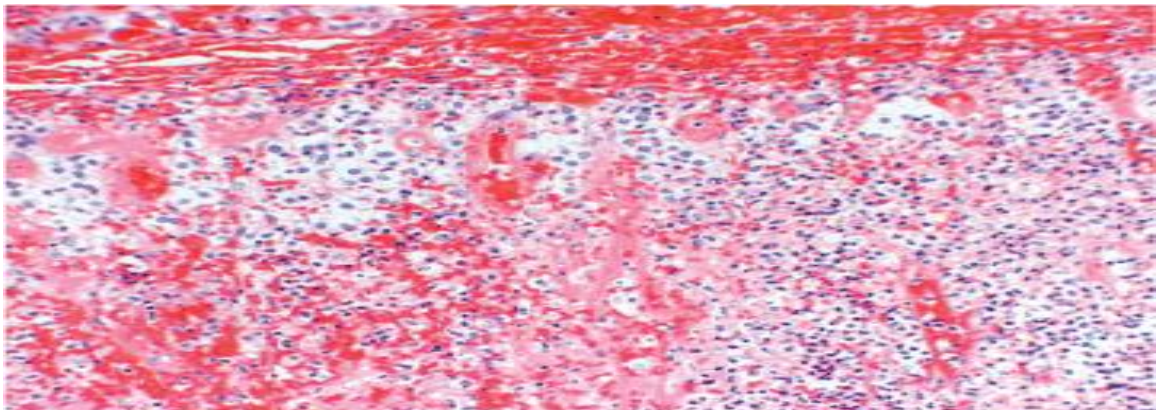
Addison disease, or chronic adrenocortical insufficiency, is an uncommon disorder resulting from progressive destruction of the adrenal cortex (90%) of the adrenal cortex has been compromised.

Symptoms described by Thomas Addison in 1855:

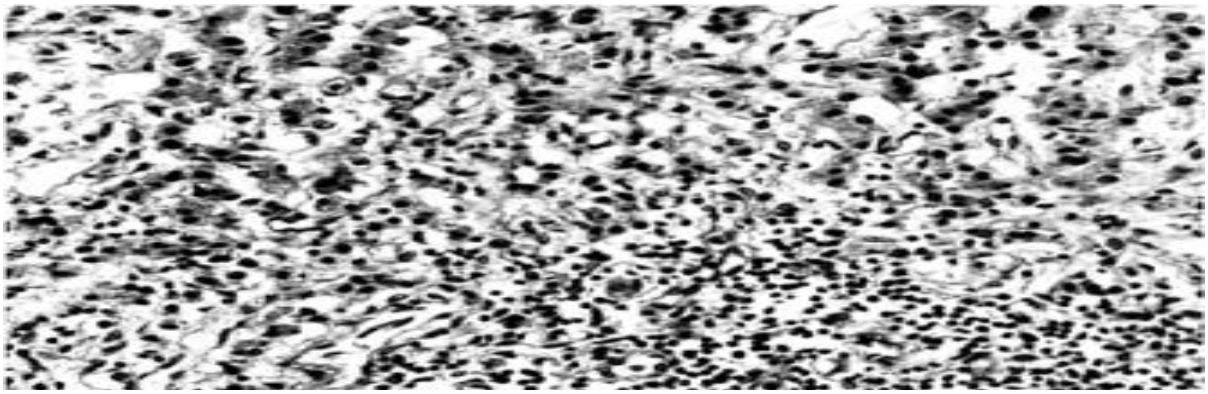
1. general languor (tiredness) and debility (weakness)
2. remarkable feebleness of the heart's action
3. change in the color of the skin"

Incidence:

Addison disease (cause by autoimmune adrenalitis) occurs mainly in whites especially women.



Acute adrenal insufficiency caused by severe bilateral adrenal hemorrhage in a waterhouse-Friderichsen syndrome. At autopsy, the adrenals were grossly hemorrhagic and shrunken; microscopically, little residual cortical architecture is visible.



Microscopic picture of autoimmune adernalitis showing an extensive mononuclear cell infiltrate

4. Pheochromocytoma:

Definition: Pheochromocytomas are neoplasms composed of chromaffin cells which secrets catecholamines and, in some case other peptides or steroids and so may be associated with Cushing syndrome or some other endocrinopathy.

They (like aldosterone-secreting adenomas) give rise to surgically correctable forms of hypertension.

Prognosis:

Only 0.1% to 0.3% (fatal) if the pheochromocytoma goes unrecognized.

Characteristics:

Pheochromocytomas usually subscribes *to "rule of 10s":*

- 10% of pheochromocytomas arise in association with one of several familial syndromes MEN-2A and MEN-2B syndromes as well as Von Hippel-Lindau, type 1 Neurofibromatosis, and Sturge-Weber syndrome (will be discussed later)
- 10% of pheochromocytomas are extra-adrenal (e.g: in carotid body it is called paragangliomas)
- 10% of nonfamilial adrenal pheochromocytomas are bilateral; this figure may rise to 70% in cases that are associated with familial syndromes.
- 10% of adrenal pheochromocytomas are biologically malignant
- 10% of adrenal pheochromocytomas in childhood (male preponderance)

The non-familial pheochromocytomas most often occur in adults between 40 and 60 years of age, with a slight female preponderance.

Morphology: (also used as criteria for paranganglioma diagnosis):

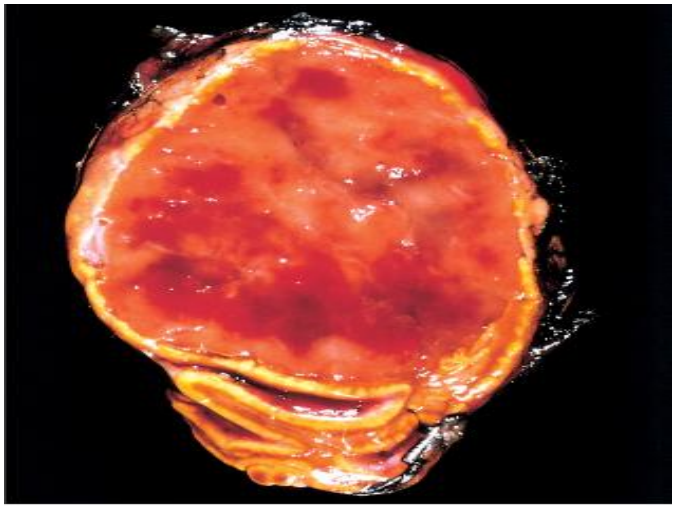
Grossly:

- Range from Small to large, hemorrhagic masses
- Well demarcated, but may show pleomorphism

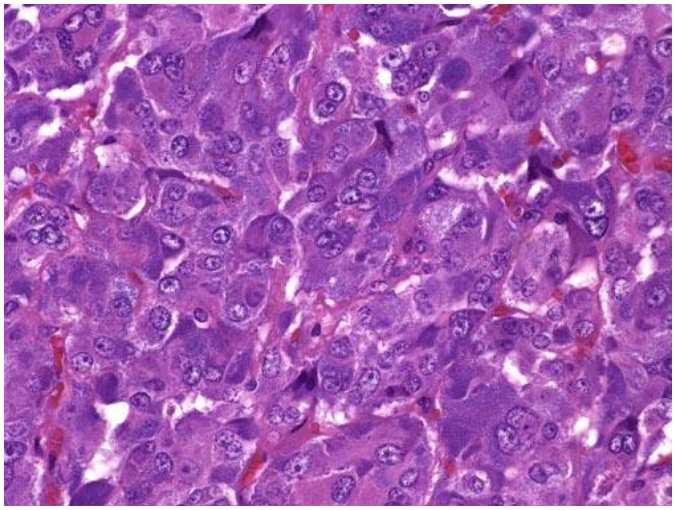
Microscopically:

Zellballen nests: which are polygonal to spindle shaped chromaffin (chief) cells mixed with Sustentacular (supporting) cells separated from other nests with a vascular network.

N.B: There is no single histologic feature that can reliably predict clinical behavior in pheochromocytomas. Even capsular and vascular invasion may be encountered in benign lesions. **Therefore, the definitive diagnosis of malignancy in pheochromocytomas is based exclusively on the presence of metastases.** These may involve regional lymph nodes as well as more distant sites, including liver, lung, and bone.



The tumor is enclosed within an attenuated cortex and demonstrates areas of hemorrhage. The comma-shaped residual adrenal is seen below



The microscopic picture shows the characteristic nests of cells ("Zellballen") with abundant cytoplasm

Syndromes: (important)

1. **Multiple Endocrine Neoplasia (MEN) type 2:**

The MEN syndromes are a group of inherited diseases resulting in proliferative lesions (hyperplasias, adenomas, and carcinomas) of multiple endocrine organs.

MEN type 2 is actually two distinct groups of disorders (type 2A and type 2B) that are unified by the occurrence of activating mutations of the *RET* protoncogene. The different mutations of different genes are possibly the cause for the different syndromes.

- Type 2A :

Organs commonly involved are:

1. Thyroid: Medullary thyroid carcinomas and C-cell hyperplasia
2. Adrenal medulla: Pheochromocytomas and adrenal medullaryhyperplasia
3. Parathyroid: Parathyroid hyperplasia with primary hyperparathyrodism

- Type 2B**:**

Organs commonly involved include:

1. The thyroid: Medullary thyroid carcinomas and C-cell hyperplasia
2. The adrenal medulla: Pheochromocytomas and adrenal medullary hyperplasia

3. The two syndromes are similar with regard to organ involvement, except that in MEN 2B there is:

- No primary hyperparathyroidism
- Develop extra endocrine manifestation such as Mucosalneuromas and Marfanoid features

2. Von Hippel-Lindau:

1. Patients suffer from renal, hepatic, pancreatic, and epididymal cysts
2. Have strong tendency to develop renal cell carcinomas,
3. Angiomatosis
4. Cerebellar hemangioblastomas

3. Type 1 Neurofibromatosis: (was previously known as von Recklinghausen disease)

1. Cutaneous hyperpigmented macules (Café au lait skin spots).
2. Schwannomas.
3. Meningiomas.
4. gliomas of the optic nerve**.**

4. Sturge-Weber syndrome:

Associated with Cavernous hemangiomas of fifth cranial nerve distribution