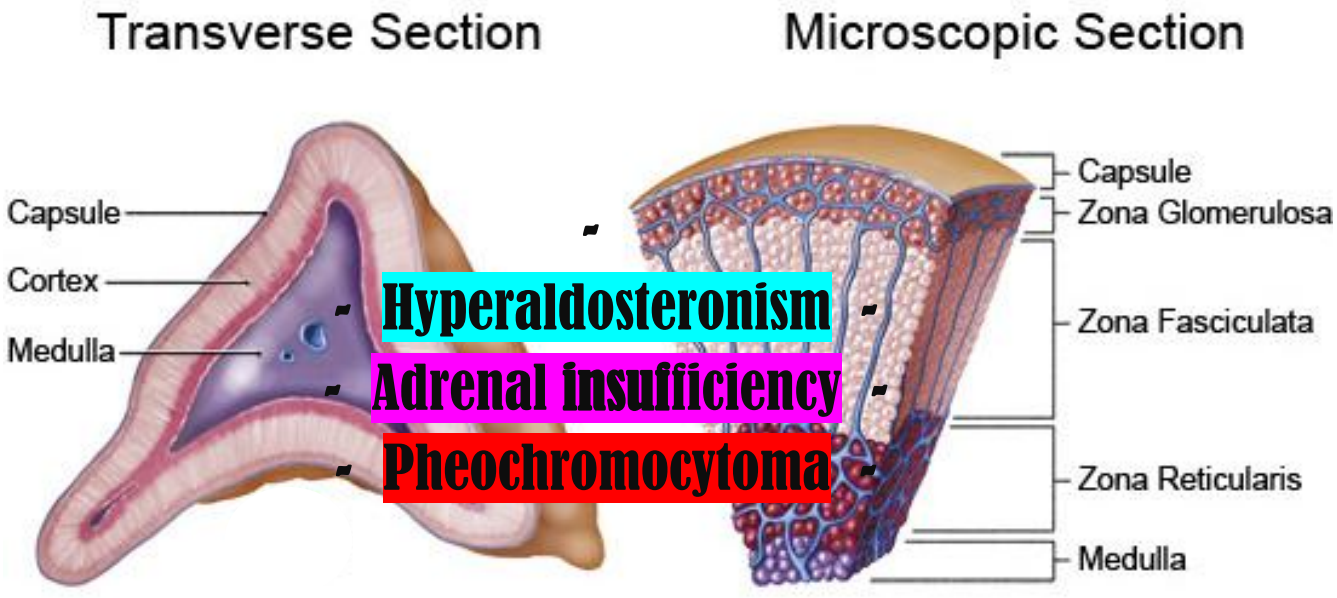
429 pathology team represents;

PATHOLOGY OF THE ADRENAL GLAND

FULLY REVISED WITH DR.HALA KFOURI



- Hyperaldosteronism
- Adrenal insufficiency
- Pheochromocytoma

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I. Hyperaldosteronism

Excessive levels of aldosterone that causes:

- *Na retention (Hypernatremia)*
- *K excretion (Hypokalemia)*

} Results with: **Hypertension**

1) Primary:

Autonomous overproduction of aldosterone, **that** results with:

A) Suppression of the *Renin-Angiotensin System.*

B) Decreased *Plasma Renin Activity.*

Causes:

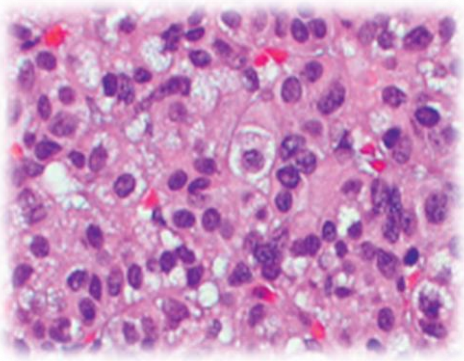
- Aldosterone-producing **adrenocortical** neoplasm, usually an adenoma (Conn's Syndrome)
- Primary adrenocortical hyperplasia,
  characterized by bilateral nodular hyperplasia, very similar to those found in the nodular hyperplasia of Cushing syndrome.
- Idiopathic. These may be caused by overactivity of the *Aldosterone Synthase Gene*.

Conn's Syndrome:

Primary hyperaldosteronism caused by an *Aldosterone-Secreting Adenoma* in one adrenal gland

The Clinical Manifestations:

- More common in *females* than in males (2:1)
- Thirties and forties **(mid-adult)**
- Most important manifestation: is Hypertension
- Hypokalemia.
- Serum renin levels are low



Morphology

GROSS:

- Solitary
- Small (<2 cm in diameter)
  Buried within the gland and *do not produce visible enlargement*
- Well-circumscribed lesions left > right
- bright yellow on cut section

Adenomas do not usually suppress ACTH secretion. Therefore, the adjacent adrenal cortex and that of the contralateral gland *are not atrophic*.

((Normally, when there is a suppression on the ACTH release by negative feedback, the other normal tissue would undergo atrophy due to low stimulation – but negative feedback on ACTH is only achieved by Cortisone and it is in normal levels here))

MICROSCOPY:

Cortical cells (***Zona Glomerulosa cells*** **–** *the normal source of aldosterone* - start to resemble zona Fasciculata cells)

Tend to be uniform in *size* (mature cortical cells) and differ from normal cells by:

Spironolactone bodies:
eosinophilic, laminated cytoplasmic *inclusions* .
((found after treatment with the antihypertensive drug *spironolactone*))

2) Secondary:

Aldosterone release occurs *in response to* activation of the renin-angiotensin system.

Characterized by increased levels of plasma renin ((while in primary *Renin is low in plasma)*

Secondary to:

- Decreased renal perfusion
  (arteriolar nephrosclerosis, renal artery stenosis)
- Arterial hypovolemia and edema
  (congestive heart failure, cirrhosis, nephrotic syndrome)
- Pregnancy (caused by *estrogen-induced* increases in plasma renin substrate).

How to differentiate between Secondary and primary *Hyperaldosteronism?*
Plasma Renin is LOW **in primary and** HIGH **in secondary.**

II. Adrenal Insufficiency:
Acute (Adrenal Crisis):

Any lesion in the *Adrenal Cortex* **that impairs** *Glucocorticoids Production* **in an** acute **way.**

*Causes:

- **Sudden** increase **in** *Glucocorticoid Requirements* **in patients with an already** *Chronic adrenocortical insufficiency (addison's disease).*
  ((patients would start with Addison's Disease then they go through *stress* and exhaust their reserves of the hormones so they'd then develop Adrenal Crisis))

- **Rapid** Withdrawal **of** *Steroids* **(when taking high doses of them)**
  ((any long-term *glucocorticoid therapy* would result in Adrenal Suppression and an inability of the adrenal gland to produce steroids on its own))

- Massive Destruction of the Adrenals **or** *Any type of adrenal hypoplasia*(1)
  (e.g. Acute hemorrhagic necrosis - ***Waterhouse-Friderichsen syndrome*** (2) – *and congenital adrenal hypoplasia*).

(1): **Any type of** Adrenal Hypoplasia:
- X-linked: A) **DAX-1 gene**
  B) **ALD gene**
  (Adrenoleukodystrophy).
- *Miniature* **(idiopathic)** type.

(2): (WFS) an **Overwhelming Sepsis** of:
1) Rapidly progressive **Hypotension** and ***Shock***
2) Disseminated Intravascular Coagulation (DIC)
3) **Massive Adrenal Hemorrhage** → ***Adrenal insufficiency***

Caused by the infections:
- **Meningococci** - or less commonly P.Pneumococci

Chronic (Addison's Disease)

An uncommon disorder resulting from *Progressive Destruction* of the adrenal cortex**.**

Causes:

- MAJOR CONTRIBUTORS
  - Autoimmune adrenalitis:
    Accounts for majority of cases (60-70%) in 3 clinical settings:
    1- Autoimmune Poly-endocrinopathy Syndrome type 1 (APS1)
    is a mutation of *AIRE1*(autoimmune regulator-1) **gene**.
    2- APS2
    (Polygenic: **2 or more genes mutation resulting in a combination of:** *Adrenal Insufficiency* **+** *Autoimmune Thyroiditis***)**
    3- Isolated Autoimmune Adrenal disease (adrenalitis) **also polygenic.**
  - Infections **(*WFS mostly by meningococcus*)**: Tuberculosis **(fungi)**
  - AIDS
  - Systemic amyloidosis
  - Sarcoidosis
  - Hemochromatosis

- MINOR CONTRIBUTORS
  - **Metastatic Carcinoma**
  - Rare genetic disorders **causing congenital adrenal hypoplasia.**
  - Same *Acute* causes *

Any factor leading to adrenal destruction

Symptoms:

- General languor **and debility (weakness)**
- **remarkable weakness of the heart's action**
- **Change in the color of the skin" → it becomes darker**

Although all races and both sexes may be affected, certain causes of Addison disease (such as autoimmune adrenalitis) are much more common in whites, particularly in women

Adrenal Neoplasms:
Could be both **Benign** or **Malignant** also **Active** (produce hormones) or **Inactive** (doesn't produce hormones). And according to the **location:**

- **Cortex Tumors**
- **Medullary Tumors** most malignant with 2 common types:
  1- **Neuroblastoma** (Small Round Cell Tumor)
  2- **Pheochromocyoma**

Pheochromocytoma

Uncommon neoplasms composed of chromaffin cells, which synthesize and release catecholamines and in some instances, peptide hormones.

- ↑↑↑ Catecholamines → Surgically-correctable hypertension.
  which may be fatal if the tumor went unrecognized. (Cardinal-sign for *Pheochromocytomas*).
- ↑↑↑ Peptides/Steroids → associated with *Cushing's syndrome* and other *Endocrinopathy*.

Etiology:

Rule of 10s:

- 10% is associated with MEN-2A and MEN-2B syndrome (MEN; multiple endocrine neoplasia)
- 10% are *Extra-adrenal*
  (arise from other locations and they will be called Pregangliomas to be distinguished)
- 10% of non-familial and 70% of familial are *Bilateral*.
- 10% of these neoplasms are "biologically malignant".
  (extradrinals are frank malignant and *hypertension* is a fatal complication of both benign & malignant ones)
- 10% of familial ones arise in *Childhood* (especially in *males*)
  while non-familial ones arise in *adulthood* (especially in *females*)

MEN-2A Syndrome Components	MEN-2B Syndrome Components
1. Thyroid Carcinoma and C-Cell Hyperplasia. 2. Pheochromocytomas 3. Adrenal Medullary Hyperplasia 4. Parathyroid Hyperplasia	1. Medullary Thryoid Carcinoma and C-Cell Hyperplasia 2. Pheochromocytomas 3. Adrenal Medullary Hyperplasia 4. Mucosal Neuromas 5. Marfanoid Features (Marfan's syndrome)[1]

(1): Is a genetic disorder of the connective tissue. It is inherited as a dominant trait. It is carried by a gene called FBN1, which encodes a connective protein called fibrillin-1.

People with Marfan's tend to be unusually tall, with long limbs and long, thin fingers. Marfan syndrome has a range of expressions, from mild to severe. The most serious complications are defects of the heart valves and aorta. It may also affect the lungs, eyes, the dural sac surrounding the spinal cord, skeleton and the hard palate.

Associated Pathology:

- Von-Hippel-Lindau disease (VHL) or Angiomatosis[2]
  (([2] a rare, autosomal dominant genetic condition in which hemangioblastomas are found in the cerebellum, spinal cord, kidney and retina. Resulting from a mutation in VHL-tumor suppressor gene))

- Renal, hepatic, pancreatic, and epididymal cysts, and Renal cell carcinomas

- Von Recklinghausen Neurofibromatosis[3] (neurofibromin type 1)
  ((3) a tumor disorder that is caused by the malfunction of a gene on chromosome 17 that is responsible for control of cell division. It causes non-cancerous lumps and often comes with scoliosis (curvature of the spine), learning difficulties, eye problems, and epilepsy))
  With Café au lait skin spots, Schwannomas, meningiomas and gliomas.

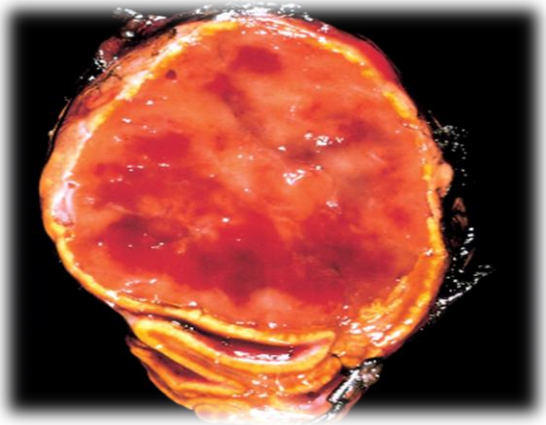
- Sturge-Weber: Cavernous hemangiomas of fifth cranial nerve distribution.

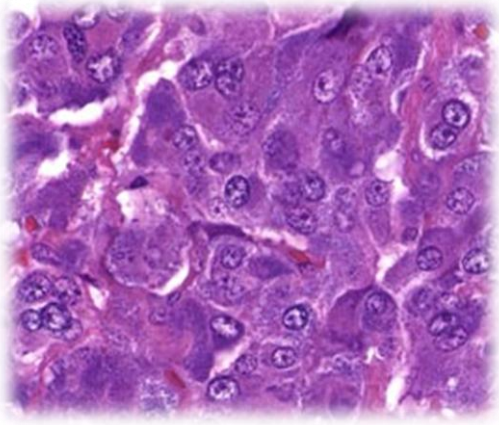
Morphology:

GROSS:

Range from small to large, and if:

Small: are circumscribed lesions that are yellow-tan confined to the adrenal.
Large: are *hemorrhagic, necrotic,* cystic masses that are *Well-demarcated* with a C.T surface.





MICROSCOPY:

Quite variable, Composed of:

Zellballen Nests

- Polygonal to spindle-shaped **chromaffin cells** or **chief cells.**
  ((termed chromaffin because they turn **brown-black**
  - due to ***Oxidized Catecholamines*****))**
- **Sustentacular small cells.**

Clustered into ***Small nests*** (or ***alveoli***)

Done ☺