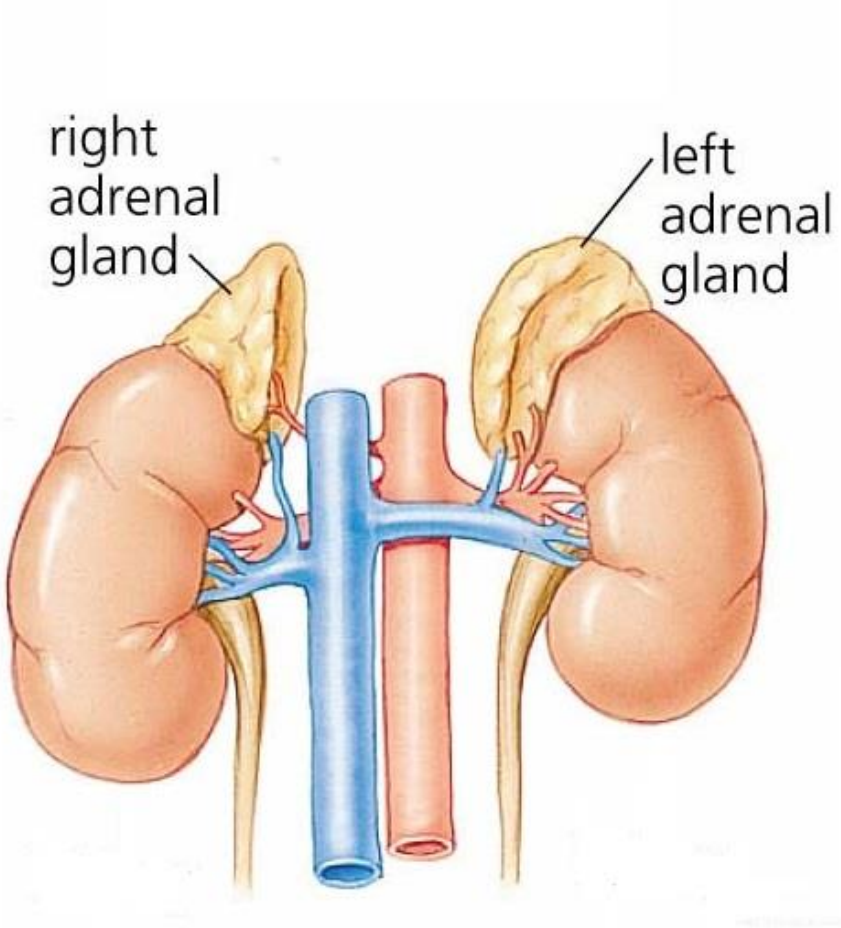
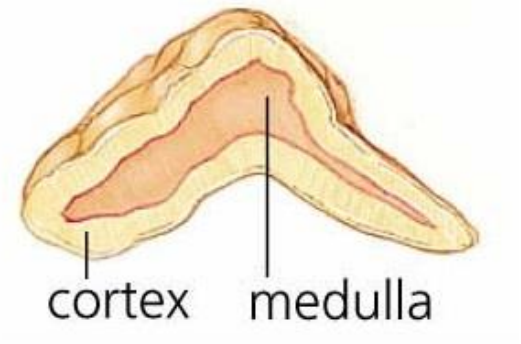




Lecture Three

Adrenal Glands

432 ***Pathology*** *Team*

Done By: Latifah *Al-Fahad &* ***Manar*** *Al-Eid*

Reviewed By: Ali *Saeed Al-Rawdhan*

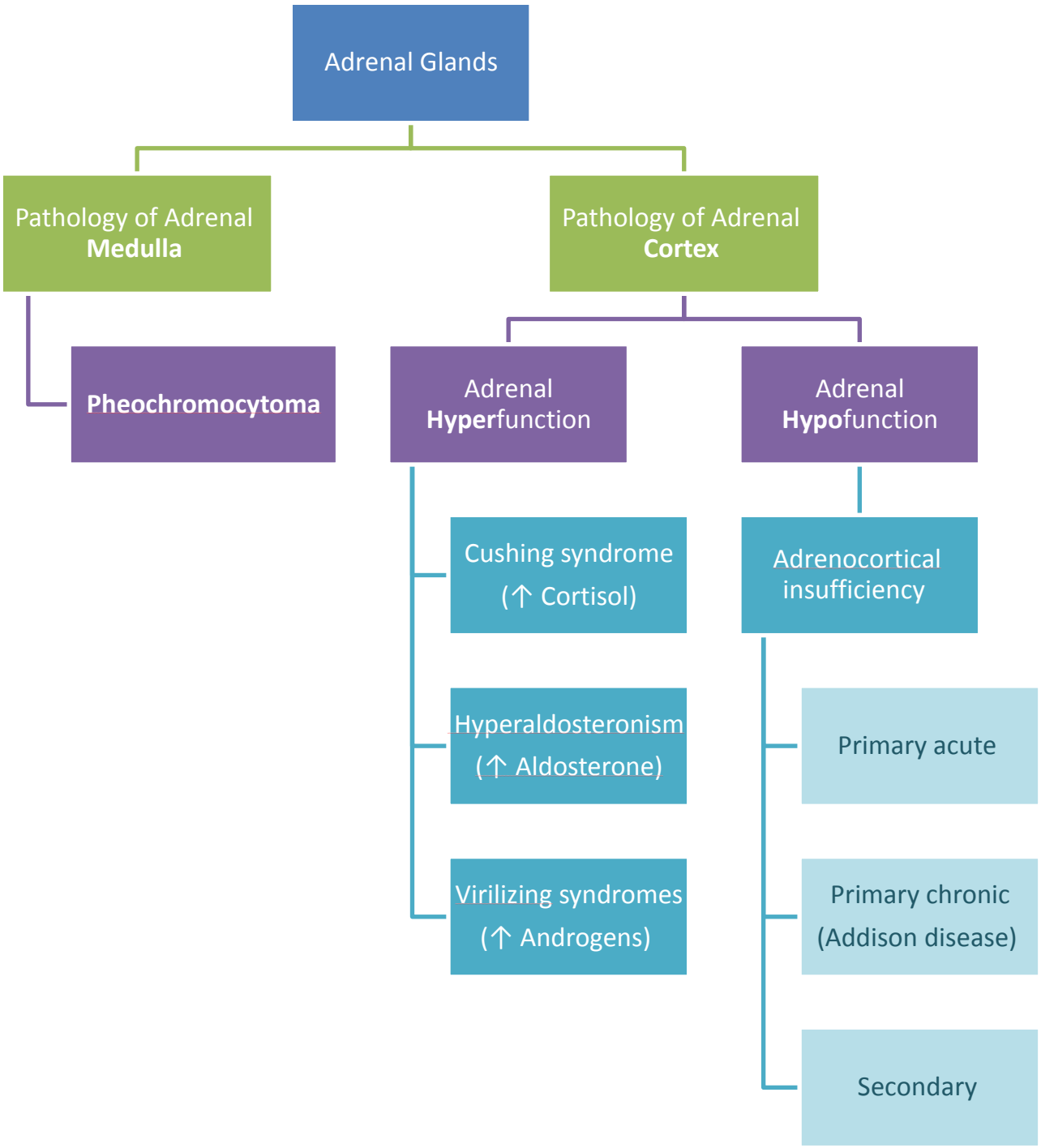
Endocrine Block

King Saud University 1957 جامعة الملك سعود

Color Index: Female notes are in Green. Male notes are in Blue. Red is important. Orange is explanation.

Pathology of Adrenal Glands

Mind Map:



Normal Adrenal Glands

Adrenal Glands:

Paired endocrine organs. Consist of cortex and medulla (4 layers: 3 cortical and 1 medullary).

1. **Cortex:**

Three layers	Three types of steroids
Zona glomerulosa	Mineralocorticoids (aldosterone)
Intervening is the broad zona fasciculata. (75%) of the total cortex.	Glucocorticoids (principally cortisol)
Zona reticularis abuts the medulla.	Sex steroids (estrogens and androgens

2. **Medulla:**

Chromaffin cells: synthesize and secrete catecholamines, mainly epinephrine.

Pathology of Adrenal Cortex: Hyperfunction (HYPERADRENALISM)

- Three basic types of corticosteroids (glucocorticoids, mineralocorticoids, and sex steroids).
- Three distinctive hyperadrenal syndromes:

1. **Cushing syndrome**, characterized by **increased cortisol**.
2. **Hyperaldosteronism**.
3. **Adrenogenital or virilizing syndromes** caused by an **excess of androgens.**

1- Cushing Syndrome (Hypercortisolism)

Broadly divided into **exogenous and endogenous** causes:

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

ACTH-Dependent:

A. **Cushing's disease** (pituitary adenoma; rarely CRH-dependent pituitary hyperplasia).
B. Ectopic corticotropin syndrome (ACTH-secreting pulmonary **small-cell carcinoma, bronchial carcinoid**).

ACTH-Independent:

A. Adrenal Adenoma.
B. Adrenal Carcinoma.
C. Macronodular hyperplasia (ectopic expression of hormone receptors, including GIPR, LHR, vasopressin and serotonin receptors).

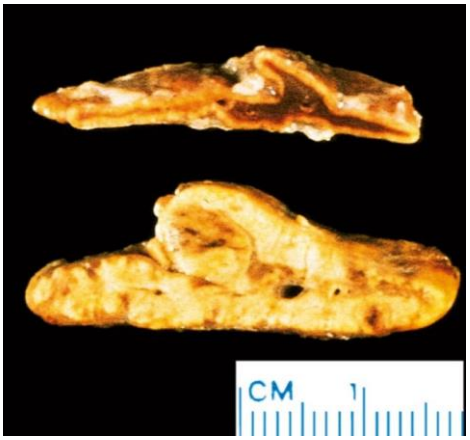
Other endogenous causes:

D. Primary pigmented nodular adrenal disease (PRKARIA and PDE11 mutations)
E. McCune-Albright syndrome (GNAS mutations)

Morphology of Hypercortisolism:

Could be one of the following abnormalities:

1. **Cortical atrophy**: results from **exogenous glucocorticoids**
2. **Diffuse hyperplasia**: individuals with **ACTH-dependent Cushing's syndrome**
3. **Macronodular** (less than 3cm), or **micronodular**(1-3mm) hyperplasia
4. **Adenoma or carcinoma**



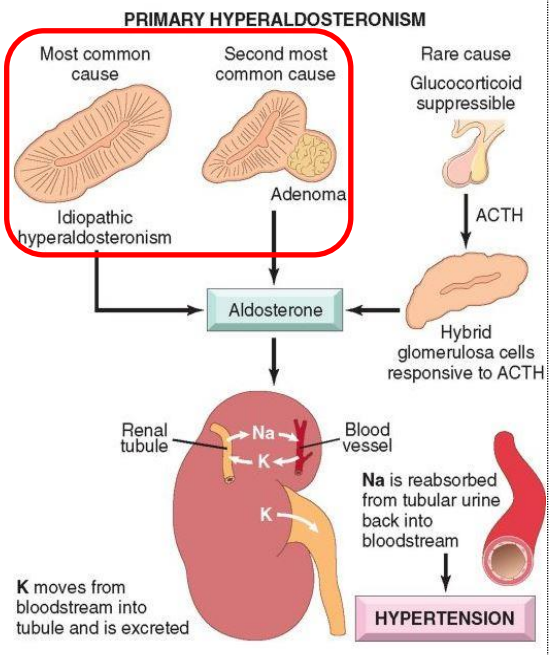
Diffuse Cortical Hyperplasia (Bottom)

Clinical Features of Cushing Syndrome:

1. Obesity or weight gain
2. Facial plethora
3. Rounded face **(Moon face)**
4. Decreased libido
5. Thin skin
6. Decrease in linear growth in children
7. Menstrual irregularity
8. Hypertension
9. Hirsutism
10. Depression/emotional liability
11. Easy bruising
12. Glucose intolerance
13. Weakness
14. Osteopenia or fracture
15. Nephrolithiasis

More commonly seen

2- Hyperaldosteronism



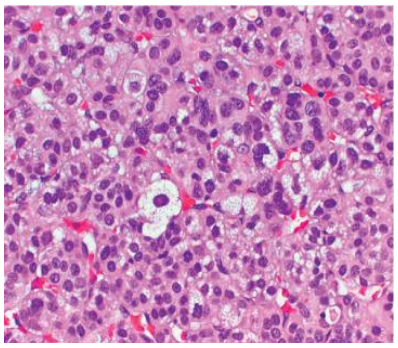
Excess aldosterone secretion, could be:

1. **Primary hyperaldosteronism** (autonomous overproduction of aldosterone) with resultant **suppression of the renin-angiotensin system** and decreased plasma renin activity.
2. **Secondary hyperaldosteronism**, in contrast, aldosterone release occurs in response to **activation of the renin-angiotensin system.**

*Whenever the Renin is HIGH, the Aldosterone must be HIGH.
*The 2ry hyperaldosteronism characterized by increased levels of plasma renin and is encountered in conditions such as the following: Decreased renal perfusion (arteriolar nephrosclerosis, renal artery stenosis) Arterial hypovolemia and edema (congestive heart failure, cirrhosis, nephrotic syndrome) Pregnancy (due to estrogen-induced increases in plasma renin substrate).

Morphology of Aldosterone-producing adenomas:

- Solitary.
- Small (<2 cm in diameter), bright yellow on cut section.
- Well-circumscribed lesions **on the left more than the right adrenal**.
- Thirties and forties.
- Women more often than in men.
- Buried within the gland and do not produce visible enlargement.
- Bright yellow on cut section.


Adenoma: Vacuolated cytoplasm

Clinical Features of Hyperaldosteronism:

- Presents with **hypertension**. With an estimated prevalence rate of 5% to 10% among non-selected hypertensive patients.
- Primary hyperaldosteronism may be the most common cause of secondary hypertension (i.e., hypertension secondary to an identifiable cause).
- Aldosterone promotes **sodium reabsorption**.
- **Hypokalemia** results from renal potassium wasting.

Pathology of Adrenal Cortex: Hypofunction

Adrenocortical Insufficiency

Caused by either:

- Primary adrenal disease (Primary hypoadrenalism).
- Or decreased stimulation of the adrenals due to a deficiency of ACTH (secondary hypoadrenalism).

TABLE 24-10 -- Adrenocortical Insufficiency

PRIMARY INSUFFICIENCY
Loss of Cortex
Congenital adrenal *hypo*plasia
X-linked adrenal hypoplasia (*DAX1* gene on Xp21)
"Miniature"-type adrenal hypoplasia (unknown cause)
Adrenoleukodystrophy (*ALD* gene on Xq28)
Autoimmune adrenal insufficiency
Autoimmune polyendocrinopathy syndrome type 1 (*AIRE1* gene on 21q22)
Autoimmune polyendocrinopathy syndrome type 2 (polygenic)
Isolated autoimmune adrenalitis (polygenic)
Infection
Acquired immune deficiency syndrome
Tuberculosis
Fungi
Acute hemorrhagic necrosis (*Waterhouse-Friderichsen syndrome*)
Amyloidosis, sarcoidosis, hemochromatosis
Metastatic carcinoma
Metabolic Failure in Hormone Production
Congenital adrenal *hyper*plasia (cortisol and aldosterone deficiency with virilization)
Drug- and steroid-induced inhibition of ACTH or cortical cell function
SECONDARY INSUFFICIENCY
Hypothalamic Pituitary Disease
Neoplasm, inflammation (sarcoidosis, tuberculosis, pyogens, fungi)
Hypothalamic Pituitary Suppression
Long-term steroid administration
Steroid-producing neoplasms

Three patterns of adrenocortical insufficiency

(1) Primary *acute* adrenocortical insufficiency (adrenal crisis)
(Like in rapid withdrawal of the steroids or failure to increase the steroid doses in response to an acute stress may lead to adrenal crisis).
(Most of time it will affect both glands).

(2) Primary *chronic* adrenocortical insufficiency *(Addison disease)*, and

(3) Secondary adrenocortical insufficiency.

Acute Adrenocortical insufficiency:

- ❖ Persons with chronic adrenocortical insufficiency may develop an acute crisis after any stress.
- ❖ This condition may occur in patients maintained on:

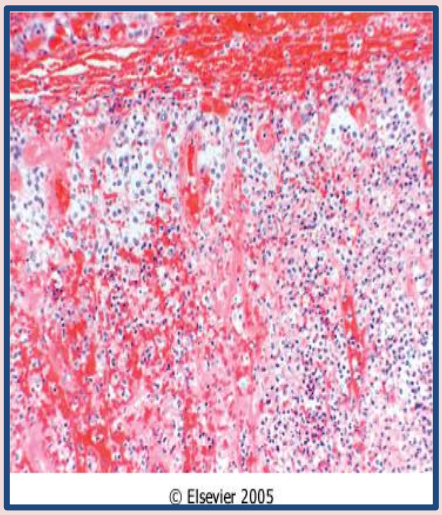
- anti-coagulant therapy.
- in postoperative patients who develop disseminated intravascular coagulation(during pregnancy).
- In patients with sepsis (waterhouse-friderichsen syndrome).

Waterhouse-Friderichsen syndrome

At autopsy, the adrenals were grossly hemorrhagic and shrunken; microscopically, little residual cortical architecture is discernible

From Robbins:

- **This syndrome is classically associated with Neisseria Meningitidis but can also be caused by other organisms.**
- **The pathogenesis remains unclear but probably involves endotoxin-induced vascular injury.**



Pathology of Adrenal Medulla

Pheochromocytoma

- ❖ Pheochromocytomas (chromaffin cells) catecholamines.
- ❖ Similar to aldosterone-secreting adenomas, give rise to surgically correctable forms of hypertension.
- ❖ 0.1% to 0.3 %(fatal).

"Rule of 10s":

- 10% of pheochromocytomas arise in association with one of several familial syndromes MEN-2A and MEN-2B syndromes.
- 10% of pheochromocytomas are extra-adrenal.
- 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.

MEN-2 Syndromes "are inherited in an autosomal pattern"

Components:
Medullary thyroid carcinomas and C-cell hyperplasia, Pheochromocytomas and adrenal medullary hyperplasia. (All these components are found in both types 2A & 2B)

- **MEN-2A:** Parathyroid hyperplasia**.**
- **MEN-2B:** Mucosal neuromas, **Marfanoid** features "remember tall and thin guy".

REMEMBER:

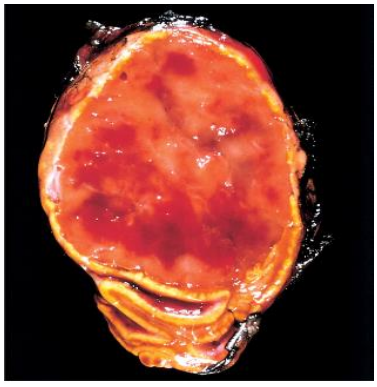
- **MEN-2A: organs commonly involved include:**
  1-Thyroid: medullary carcinoma
  2-Adrenal Medulla: Pheochromocytoma.
  3-Parathyroid: parathyroid hyperplasia**.**
- **MEN-2B: organs commonly involved include the thyroid and the adrenal Medulla.**
  1- Associate with Extra-endocrine manifestations.
  (All persons carrying RET mutations are advised to have prophylactic thyroidectomy to prevent the development of medullary carcinomas).

Complications of Pheochromocytoma:

- **Von Hippel-Lindau**: Renal, hepatic, pancreatic, and epididymal cysts, Renal cell carcinomas, Angiomatosis, Cerebellar hemangioblastomas, DM
- **Von Recklinghausen Neurofibromatosis**: Café au lait skin spots, Schwannomas, meningiomas, gliomas
- **Sturge-Weber**: Cavernous hemangiomas of fifth cranial nerve distribution

Morphology

- Small to large hemorrhagic
- Well demarcated
- Polygonal to spindle shaped (chromaffin, chief cells)
- Sustentacular small cells
- Together, Zellballen nests


© Elsevier 2005

Summary from Robbins:

- The most common cause of hypercortisolism is exogenous administration of steroids.
- Endogenous hypercortisolism most often is secondary to an ACTH-producing pituitary microadenoma (Cushing disease), followed by primary adrenal neoplasms (ACTH-independent hypercortisolism) and paraneoplastic ACTH production by tumors (e.g., small cell lung cancer).
- The morphologic features in the adrenal include bilateral cortical atrophy (in exogenous steroid-induced disease), bilateral diffuse or nodular hyperplasia (most common finding in endogenous Cushing syndrome), or an adrenocortical neoplasm.
- The adrenal cortex can secrete excess androgens in ether of two settings: adrenocortical neoplasms (usually virilizing carcinomas) or congintal adrenal hyperplasia (CAH).
- CAH consists of a group of autosomal recessive disorders characterized by defects in steroid biosynthesis, usually cortisol; the most common subtype is caused by deficiency of the enzyme 21-hydroxylaze.
- Reduction in cortisol production causes a compensatory increase in ACTH secretion, which in turn stimulates androgen production. Androgens have virilizing effects, including masculinization in females (ambiguous gentialia, oligomenorrhea, and hirsutism), precocious puberty in malesm, and in some instances, salt (Na+) wasting and hypotension.
- Bilateral hyperplasia of the adrenal cortex is characteristic.
- Primary adrenocortical insufficiency can be acute (waterhouse-friderichsen syndrome) or chronic (Addison disease).
- Chronic adrenal insufficiency in western world most often is secondary to autoimmune adrenalitis, which occurs in the context of one of two autoimmune polyendocrine syndromes: APSI (caused by mutations in the AIRE gene) or APS2.
- TB and infections due to opportunistic pathogens associated with the human immunodeficiency virus and tumors metastatic to the adrenlas are the other important cause of chronic hypoadrenalism.
- Patients typically present with fatigue, weakness, and GI disturbances. Primary adrenocortical insufficiency also is characterized by high ACTH levels with associated skin pigmentation.

Summary

<table>
<tr><th colspan="2">Adrenal cortex</th></tr>
<tr><th colspan="2">Cortisol "Hypercortisolism (cushing syndrome)"</th></tr>
<tr><td>ACTH-dependent</td><td>ACTH-independent</td></tr>
<tr><td>1- Pituitary adenoma.
2- Ectopic corticotropin syndrome.</td><td>1-Adrenal Adenoma.
2-Adrenal Carcinoma.
3-Macronodular hyperplasia.</td></tr>
<tr><td colspan="2">Clinical Features</td></tr>
<tr><td colspan="2">1. Obesity or weight gain.
2. Facial plethora.
3. Rounded face (Moon face).</td></tr>
<tr><td colspan="2">Morphology</td></tr>
<tr><td colspan="2">✳ Cortical atrophy.
✳ Diffuse hyperplasia.
✳ Macronodular or micronodular.
✳ Adenoma or carcinoma.</td></tr>
<tr><th colspan="2">Hyperaldosteronism</th></tr>
<tr><td>Primary Hyperaldosteronism</td><td>Secondary Hyperaldosteronism</td></tr>
<tr><td>- Suppression of the renin-angiotensin system.</td><td>- Activation of the renin-angiotensin system.</td></tr>
<tr><td colspan="2">Clinical Features</td></tr>
<tr><td colspan="2">*2nd hypertention-hypo (K+).</td></tr>
<tr><td colspan="2">Morphology</td></tr>
<tr><td colspan="2">Solitary-small- more in the left adrenal.</td></tr>
<tr><th colspan="2">Adrenocortical insufficiency</th></tr>
<tr><td colspan="2">(1) Primary <u>acute</u> adrenocortical insufficiency (adrenal crisis).
(2) Primary <u>chronic</u> adrenocortical insufficiency (Addison disease).
(3) <u>Secondary</u> adrenocortical insufficiency.</td></tr>
<tr><th colspan="2">Adrenal Medulla</th></tr>
<tr><th colspan="2">Pheochromocytoma</th></tr>
<tr><td colspan="2">Morphology</td></tr>
<tr><td colspan="2">Hemorrhage – Sustenticular small cells - Zellballen nests</td></tr>
</table>

Questions

1/ A 60-year-old woman with small cell carcinoma of the lung notes rounding of her face, upper truncal obesity, and muscle weakness. Physical examination reveals thin, wrinkled skin, abdominal striae, and multiple purpuric skin lesions. The patient's blood pressure is 175/95 mm Hg. Laboratory studies will likely show elevated serum levels of which of the following hormones?

(A) Aldosterone
(B) Corticotropin
(C) Epinephrine
(D) Prolactin

2/ A 46-year-old woman with severe asthma presents with increasing weight and back pain for 9 months. The patient is taking corticosteroids for her asthma. An X-ray of the vertebrae will likely reveal which of the following pathologic findings?

(A) Boneinfarct
(B) Dislocation
(C) Osteomalacia
(D) Osteoporosis

3/ A 34-year-old man complain of sudden attacks of dizziness, blurred vision, and excruciating headaches of 4 months in duration. During one of these attacks, his blood pressure was 180/120 mm Hg. The patient's father had been treated for thyroid cancer about 15 years ago. Laboratory studies show normal serum levels of aldosterone, renin, and angiotensin. A 24-hour urinalysis reveals increased metanephrines. Episodic hypertension in this patient is most likely caused by a tumor in which of the following endocrine organs?

(A) Adrenal
(B) Kidney
(C) Parathyroid
(D) Pituitary

Answers:

- 1- B
- 2- D
- 3- A

اللهم إني استودعك ما قرأت و ما حفظت و ما تعلمت فرده عليَ عند حاجتي إليه انك على كل شيء قدير

If there is any mistake or feedback please contact us on: 432PathologyTeam@gmail.com