

The Adrenal gland

I. Adrenocortical Hyperfunction (Hyperadrenalism)

1. Hypercortisolism (Cushing Syndrome)

- In clinical practice, most cases are caused by the administration of exogenous glucocorticoids (iatrogenic)
- The remaining cases are endogenous and caused by one of the following

A. Primary hypothalamic-pituitary diseases associated with hypersecretion of ACTH (Cushing disease)

- Accounts for 70% of cases of spontaneous, endogenous Cushing syndrome .
- Occurs most frequently during young adulthood (the 20s and 30s) and mainly affecting women

- In the vast majority of cases, the *pituitary gland contains an ACTH-producing microadenoma*
- In the remaining patients, the anterior pituitary contains areas of *corticotroph cell hyperplasia*
- The adrenal glands in Cushing disease show bilateral nodular cortical hyperplasia secondary to the elevated levels of ACTH ("ACTH-dependent" Cushing syndrome).
- The cortical hyperplasia, in turn, is responsible for the hypercortisolism

B. Primary adrenal hyperplasia and neoplasms

- Are responsible for about 10% to 20% of cases of endogenous Cushing syndrome and this form is called *ACTH-independent Cushing syndrome*, or adrenal Cushing syndrome and its biochemical hallmark is elevated levels of cortisol with low serum levels of ACTH
- In most cases, adrenal Cushing syndrome is caused by a unilateral adrenocortical neoplasm, which may be either benign (adenoma) or malignant (carcinoma).

- **Note-**
- The overwhelming majority of hyperplastic adrenals are ACTH-dependent, and primary cortical hyperplasia of the adrenal cortices is a rare cause of Cushing syndrome

C. Secretion of ectopic ACTH by nonpituitary tumors

- Accounts for about 10% of cases of Cushing syndrome mostly caused by *small cell carcinoma of the lung*,
- The adrenal glands undergo bilateral hyperplasia due to elevated ACTH, but the rapid downhill course of patients with these cancers cuts short the adrenal enlargement

MORPHOLOGY of the pituitary in Cushing syndrome

Crooke hyaline change :

- Results from high levels of glucocorticoids, and in this condition, the normal basophilic cytoplasm of the ACTH-producing cells is replaced by homogeneous slightly basophilic material
- This alteration is the result of the accumulation of intermediate keratin filaments in the cytoplasm.

Changes in adrenal in cases of Cushing syndrome:

1) Cortical atrophy :

- If the syndrome results from exogenous glucocorticoids ,suppression of endogenous ACTH results in bilateral cortical atrophy, due to a lack of stimulation of the zona fasciculata and reticularis by ACTH,
- The zona glomerulosa is of normal thickness because it functions independently of ACTH

2. Diffuse and nodular hyperplasia:

- Is found in 60% to 70% of Cases of endogenous Cushing syndrome.
- a-** Secondary hyperplasia is found in patients with ACTH- dependent Cushing syndrome (due to Cushing disease or ectopic production of ACTH)
- b -** In primary cortical hyperplasia, the cortex is replaced almost entirely by macro- or pigmented micronodules, and the pigment is believed to be lipofuscin

3. Primary adrenocortical neoplasms

- Are more common in women in their 30s to 50s.
- a. Adrenocortical adenomas: Are yellow tumors surrounded by thin capsules, and most weigh less than 30 g
- b. Carcinomas tend to be nonencapsulated masses , exceeding 200 to 300 g in weight,

Note:

- With both functioning benign and malignant tumors, the adjacent adrenal cortex and that of the contralateral adrenal gland are atrophic because of suppression of endogenous ACTH by high cortisol levels

Clinical Course.:

Cushing syndrome develops gradually but a major exception to this insidious onset is with Cushing syndrome associated with small cell carcinomas

Manifestations

- a. Hypertension and weight gain are early manifestations.
- b. With time, truncal obesity, "moon facies," accumulation of fat in the posterior neck and back ("buffalo hump")
- c. Selective atrophy of fast-twitch (type II) myofibers, with decreased muscle mass and proximal limb weakness.

- d. Glucocorticoids induce gluconeogenesis with resultant *hyperglycemia, glucosuria, and polydipsia*.
- e. The catabolic effects on proteins cause loss of collagen and resorption of bone and bone resorption results in *osteoporosis, and* susceptibility to fractures.
- f. The skin is thin, fragile, and easily bruised; cutaneous striae are particularly common in the abdominal area and resulted from catabolic effects on collagens in the skin

- g. Patients are at increased risk for a variety of infections.
- h. Hirsutism and menstrual abnormalities
- i. Mental disturbances ,mood swings, depression, psychosis

Note:

- Extra-adrenal Cushing syndrome caused by pituitary or ectopic ACTH secretion usually is associated with increased skin pigmentation secondary to melanocyte-stimulating activity in the ACTH precursor molecule

2. Hyperaldosteronism

1. In secondary hyperaldosteronism:

- Aldosterone release occurs in response to activation of renin-angiotensin system and characterized by increased levels of plasma renin and is encountered in conditions associated with:
 - a. Decreased renal perfusion
 - b. Arterial hypovolemia and edema like in heart failure
 - c. Pregnancy (caused by estrogen-induced increases in plasma renin substrate)

2. Primary hyperaldosteronism:

- Indicates primary , autonomous overproduction of aldosterone with secondary suppression of renin-angiotensin system and decreased plasma renin activity and the causes are:

a. *Bilateral idiopathic hyperaldosteronism,*

- Characterized by bilateral nodular hyperplasia of adrenals
- Is the most common underlying cause of primary hyperaldosteronism, accounting for about 60% of cases

- b. Adrenocortical neoplasm,
 - 1. adenoma (the most common cause)
 - 2. or, rarely, an adrenocortical carcinoma.
- In approximately 35% of primary hyperaldosteronism cases, the cause is a solitary Aldosterone-producing adrenocortical adenoma referred to as Conn syndrome
- c. Rarely, familial hyperaldosteronism may result from a genetic defect that leads to overactivity of the *aldosterone synthase* gene, *CYP11B2*.

MORPHOLOGY

1. Aldosterone-producing adenomas (Conn syndrome)
 - a. Are solitary yellow lesion,
 - b. less than 2 cm in diameter ,
 - c. Composed of lipid-laden cells more closely resembling fasciculata cells
- The cells tend to be uniform in size and shape; with occasional nuclear and cellular pleomorphism.

- A characteristic feature of aldosterone-producing adenomas is the presence of eosinophilic, laminated cytoplasmic inclusions, known as spironolactone bodies
- These typically are found after treatment with the antihypertensive agent spironolactone, which is the drug- of choice in primary hyperaldosteronism.

Note:

- Adenomas associated with hyperaldosteronism do not suppress ACTH secretion; therefore, the adjacent cortex and that of the contralateral gland are not atrophic

2. Bilateral idiopathic hyperplasia:

- Hyperplasia of cells resembling those of the normal zona glomerulosa. often occurs in children and young adults

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Clinical Features :

1- *The clinical hallmark is hypertension*

- Hyperaldosteronism may be the most common cause of secondary hypertension

2- *Hypokalemia* results from renal potassium wasting and, can cause neuromuscular manifestations, including weakness, paresthesias,, and occasionally frank tetany.

- Adenomas are amenable to surgical excision.
- Surgical intervention is not very beneficial in bilateral hyperplasia, and best managed medically with *analdosterone antagonist* such as spironolactone
- The treatment of secondary hyperaldosteronism rests on correcting the underlying cause of the renin-angiotensin system hyperstimulation.

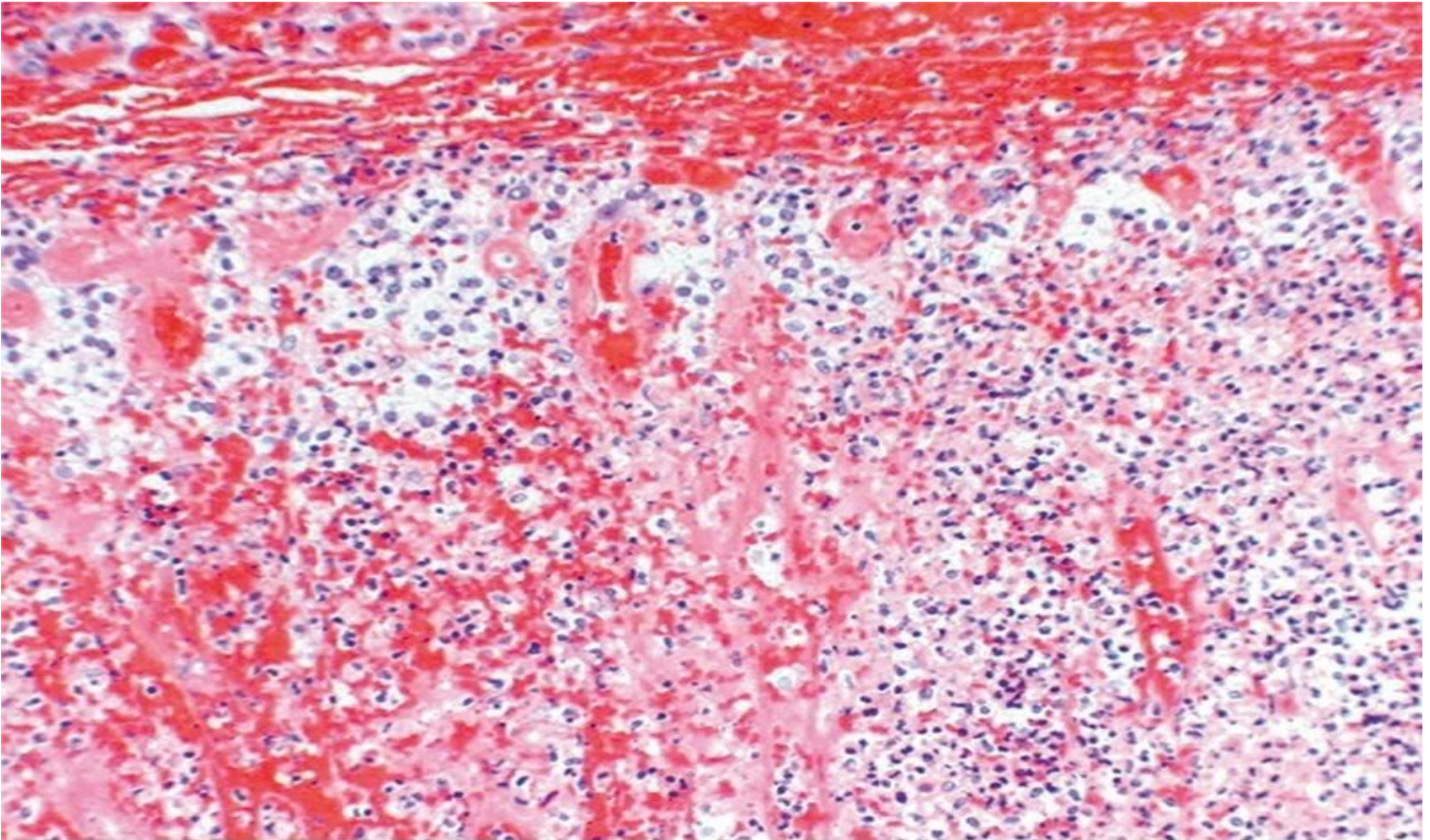
ADRENAL INSUFFICIENCY :The patterns are:

1. Acute Adrenocortical Insufficiency : causes

- a. Crisis in patients with chronic adrenocortical insufficiency precipitated by stress
- b. In patients maintained on exogenous corticosteroids, rapid withdrawal of steroids or failure to increase steroid doses in response to an acute stress, because of the inability of the atrophic adrenals to produce glucocorticoid
- c. *Massive adrenal hemorrhage* may destroy enough of the adrenal cortex to cause acute adrenocortical insufficiency

- This condition may occur :
 1. In patients maintained on anticoagulant therapy
 2. Patients suffering from sepsis : a condition known as the Waterhouse-Friderichsen syndrome
- This catastrophic syndrome is associated with *Neisseria meningitidis* septicemia but can also be caused by *Pseudomonas* spp., , and *Haemophilus influenzae*
- The pathogenesis remains unclear but probably involves endotoxin-induced vascular injury

Adrenal hemorrhage



2. Primary Chronic Adrenocortical Insufficiency Called (Addison Disease):

- Is an uncommon disorder resulting from progressive destruction of the adrenal cortex.
- More than 90% of all cases are attributable to :.

a. Autoimmune adrenalitis

- Accounts for 60% to 70% of cases and is the most common cause of primary adrenal insufficiency in developed countries
- There is autoimmune destruction of steroid-producing cells, and autoantibodies to several key steroidogenic enzymes have been detected in affected patients

- Occurs in one of two *autoimmune polyendocrine* syndromes:
 1. APS1, caused by mutations in the *autoimmune regulator (AIRE)* gene on chromosome 21 and is characterized by
 - a. Chronic mucocutaneous candidiasis
 - b. Abnormalities of skin, dental enamel, and nails (ectodermal dystrophy)

- It occurs in association with a other autoimmune disorders (s, autoimmune hypoparathyroidism, that result in destruction of target organs.
- b. APS2, which manifests in early adulthood as a combination of adrenal insufficiency and autoimmune thyroiditis or type 1 diabetes.
- Mucocutaneous candidiasis, ectodermal dysplasia, and autoimmune hypoparathyroidism do not occur.

B. Infections,:

- 1- Tuberculous adrenalitis, which once accounted for as many as 90% of cases of Addison disease, has become less common with the advent of anti-tuberculosis therapy
- With resurgence of tuberculosis in many urban centers, this cause of adrenal deficiency must be borne in mind.
- When present, tuberculous adrenalitis usually associated with active infection in lungs and genitourinary tract

2- Disseminated infections caused by *Histoplasma capsulatum* and *Coccidioides immitis* also may result in chronic adrenocortical insufficiency.

Note

- Patients with AIDS are at risk for the development of adrenal insufficiency from several infectious (cytomegalovirus) and noninfectious (Kaposi sarcoma)

C- Metastatic neoplasms involving the adrenals

- Although adrenal function is preserved in most such instances, the metastatic growths sometimes destroy sufficient adrenal cortex to produce a degree of adrenal insufficiency.
- Carcinomas of the lung and breast are the source of a majority of metastases in the adrenals

Secondary Adrenocortical Insufficiency

- Caused by any disorder of the hypothalamus and pituitary, that reduces the output of ACTH such as
 - a. Metastatic cancer
 - b. Infection, infarction, or irradiation,
- ACTH deficiency may occur alone, but in some instances, it is only one part of panhypopituitarism,

Clinical manifestation of adrenocortical insufficiency

- 1- Due to the destruction of the adrenal cortex in Addison disease, there will be no response to exogenously administered ACTH in the form of increased plasma cortisol
- 2- Secondary adrenocortical insufficiency is characterized by low serum ACTH and a prompt rise in plasma cortisol levels in response to ACTH administration

- Clinical manifestations of adrenocortical insufficiency do not appear until at least 90% of the adrenal cortex has been compromised
 - a. The initial manifestations often include progressive weakness and easy fatigability .
 - b. Gastrointestinal disturbances* are common and include anorexia, nausea, vomiting, weight loss, and diarrhea

- c. In patients with primary adrenal disease, increased levels of ACTH precursor hormone stimulate melanocytes, with resultant *hyperpigmentation* of the skin and mucosal surfaces: The face, axillae, nipples, areolae, and perineum are mainly affected
- By contrast, hyperpigmentation is not seen in patients with secondary adrenocortical insufficiency.

- d. Decreased mineralocorticoid (aldosterone) activity in patients with primary adrenal insufficiency results in potassium retention and sodium loss , with consequent - *hyperkalemia, hyponatremia, volume depletion, and hypotension*
- e. In secondary hypoadrenalism ,it is characterized by deficient cortisol and androgen output but normal or near-normal aldosterone synthesis

- Hypoglycemia occasionally may occur as a result of glucocorticoid deficiency and impaired gluconeogenesis.
- Stresses such as infections, trauma, or surgical procedures in affected patients may precipitate an acute adrenal crisis, manifested by
 - a. intractable vomiting, and abdominal pain,
 - b. Hypotension, coma, and vascular collapse.
- Death follows rapidly unless corticosteroids are replaced immediately. .

TUMORS OF THE ADRENAL MEDULLA

Pheochromocytoma

- Are neoplasms composed of chromaffin cells, synthesize and release catecholamines .
- These tumors are of importance because they give rise to a surgically correctable form of hypertension.
- Pheochromocytomas usually subscribe to "rule of 10s":

- a. *10% of pheochromocytomas are extraadrenal,* occurring in sites such as the carotid body, where they usually are called *paragangliomas*, rather than pheochromocytomas
- b. *10% of adrenal pheochromocytomas are bilateral;* this proportion may rise to 50% in cases that are associated with familial syndromes.
- c. *10% of adrenal pheochromocytomas are malignant,*
 - Frank malignancy is somewhat more common in tumors arising in extraadrenal sites.

- 25% of persons with pheochromocytomas and paragangliomas harbor a germ line mutation in one of at least six known genes including:
 1. *RET*, which causes type 2 MEN syndromes
 2. *NF1*, which causes type 1 neurofibromatosis
 3. *VHL*, which causes von Hippel-Lindau disease ;
 4. Three genes encoding subunits within the succinate dehydrogenase complex (*SDHB*, *SDHC*, and *SDHD*), involved in mitochondrial oxidative phosphorylation

Gross

- Range from small, lesions confined to the adrenal to large, hemorrhagic masses weighing several kilograms
- On cut surface, smaller pheochromocytomas are yellow-, well-defined lesions that compress the adjacent adrenal
- Larger lesions tend to be hemorrhagic, necrotic, and cystic and typically efface the adrenal gland.
- Incubation of the fresh tissue with potassium dichromate solutions turns the tumor dark brown,

On microscopic examination

- Are composed of polygonal to spindle-shaped chromaffin cells and their supporting cells, compartmentalized into small nests, or **Zellballen**, by a rich vascular network
- The cytoplasm has a finely granular appearance, because of the presence of granules containing catecholamines.
- The nuclei of the neoplastic cells are often pleomorphic

Note

- Both capsular and vascular invasion may be encountered in benign lesions, and the mere presence of mitotic figures does not imply malignancy.
- 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.

Clinical Features

- The predominant clinical manifestation is *hypertension*
- The characteristic presentation with hypertensive episode is one of abrupt, precipitous elevation in blood pressure, associated with tachycardia, palpitations, headache, sweating, tremor, and a sense of apprehension
- Such episodes also may be associated with pain in the abdomen or chest, nausea, and vomiting

- In clinical practice, *isolated, paroxysmal episodes of hypertension occur in fewer than half of patients with pheochromocytoma.*
- In about two thirds of patients the hypertension occurs as a chronic, sustained elevation in blood pressure.
- Sudden cardiac death may occur, probably secondary to catecholamine-induced myocardial irritability and ventricular arrhythmias.

- In some cases, pheochromocytomas secrete hormones such as ACTH and somatostatin.
- The laboratory diagnosis of pheochromocytoma is based on demonstration of increased urinary excretion of free catecholamines and their metabolites, such as vanillylmandelic acid and metanephrines.
- Isolated benign pheochromocytomas are treated with surgical excision.
- With multifocal lesions, long-term medical treatment for hypertension may be required.

MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES

- Are a group of inherited diseases resulting in proliferative lesions) of multiple endocrine organs.
- Endocrine tumors arising in the context of MEN syndromes have certain distinctive features that are not shared with their sporadic counterparts:
 1. Occur at a *younger age* than that for sporadic cancers.
 2. They arise in *multiple endocrine organs*,

- Even in one organ, the tumors often are *multifocal*.
3. Are usually *more aggressive* and *recur* in a higher proportion of cases than tumors that occur sporadically.

MEN type 1

- Is an autosomal dominant syndrome and the gene (*MEN1*) is located at 11 and is a tumor suppressor gene;.
- Organs most commonly involved are the parathyroid, the pancreas, and the pituitary-the "3 Ps."

a. Parathyroid:

- *Primary hyperparathyroidism* is the most common manifestation of MEN-1 (80% to 95% of patients) and is the initial manifestation of the disorder appearing in almost all patients by age 40 to 50.
- Abnormalities include both hyperplasia and adenomas

b. Pancreas:

- Endocrine tumors of the pancreas are the leading cause of death in MEN-1.
- Are aggressive tumors manifest with metastatic disease.
- Pancreatic endocrine tumors often are functional
 1. - Zollinger-Ellison syndrome, associated with gastrinomas, is common and gastrinomas are more likely to be located within the duodenum than in the pancreas
 2. - Hypoglycemia, related to insulinomas, is also common

c. Pituitary:

- The most frequent pituitary tumor in patients with MEN-1 is a prolactin-secreting macroadenoma.
- In some cases, acromegaly develops in association with somatotropin-secreting tumors.

Multiple Endocrine Neoplasia Type 2A

a. Thyroid:

- Medullary carcinoma of the thyroid develops in virtually all untreated cases, and the tumors usually occur in the first 2 decades of life.-

b. Adrenal medulla: Pheochromocytomas develop in 50% of the patients; and 10% of these tumors are malignant.

c. Parathyroid:

- 10% to 20% of patients develop parathyroid hyperplasia resulting in primary hyperparathyroidism

Multiple Endocrine Neoplasia Type 2B

- Patients with MEN-2B harbor a distinct germline *RET* mutation
- a. Organs commonly involved include the thyroid and the adrenal medulla and the spectrum of thyroid and adrenal medullary disease is similar to that in MEN-2A,
- b. Primary hyperparathyroidism does not develop in patients with MEN-2B.
- c. *Extraendocrine manifestations* include :
 1. Ganglioneuromas of mucosal sites (gastrointestinal tract, lips, tongue)

2. a *marfanoid habitus*, in which overly long bones of the axial skeleton give an appearance resembling that in Marfan syndrome
- Before the advent of genetic testing, relatives of patients with the MEN-2 syndrome were screened with annual biochemical tests, which often lacked sensitivity.
 - Now, routine genetic testing identifies *RET* mutation carriers earlier and more reliably in MEN-2 kindreds;
 - All persons carrying germline RET mutations are advised to have prophylactic thyroidectomy to prevent the inevitable development of medullary carcinomas.