Pathology of adrenal gland

Objectives

- Understand the structure and function of adrenal glands.
- Know the disorders that can cause hypo or hyper function of the adrenal cortex.
- Understand the histopathological features of both medullary (pheochromocytoma) and adrenocortical neoplasms.

Black: original content
Red: Important
Green: only found in males slides

Orange: Doctor notes
Grey: Extra/Robbins
Purple: Only found in females slides

Reviewed by Razan AlRabah & Ibrahim AlDakhil

Editing File

Lecture Content

- **Hyperadrenalism**
  - Hypercortisolism cushing's
  - Hyperaldosteronism
  - Hypersecretion of androgens
- **Adrenal insufficiency**
  - Water-Friderichsen syndrome
  - Addison's disease
- **Adrenal Neoplasms**
  - Cortical Adenoma
  - Adrenocortical carcinoma
  - Pheochromocytoma

Hyperadrenalism

Introduction

- Abnormal production of one or more of the hormones produced by the adrenal cortex. Which include:
  - Cushing syndrome; hypercortisolism.
  - Hyperaldosteronism.
  - Andrenogenetalia or viralization; hyperandrogenism.

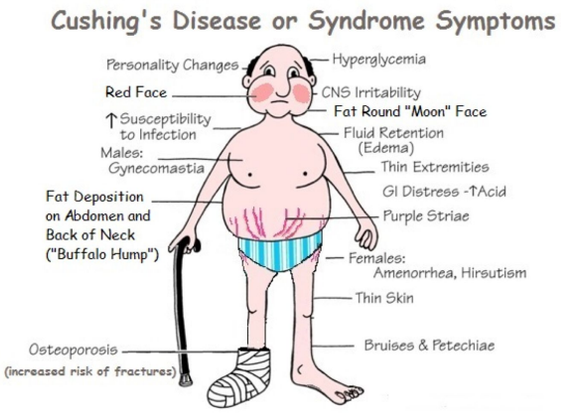
Hypercortisolism (Cushing syndrome)

- Mainly divided into:
  - **Exogenous**: due to administration of glucocorticoids (iatrogenic[1] cushing syndrome). **Most common.**
    - Cortical **Atrophy** is observed
  - **Endogenous** can then be divided into
    - ACTH- dependent: more common
      - Cushing disease.
      - Ectopic ACTH secreting SSC.
    - ACTH- independent:
      - Adrenal adenoma.
      - Adrenal 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 (ectopic expression of hormone receptors, including GIPR, LHR, vasopressin and serotonin receptors)	<2	1:1
Primary pigmented nodular adrenal disease (*PRKARIA* and *PDE11* mutations)	<2	1:1
McCune-Albright syndrome (*GNAS* mutations)	<2	1:1

Clinical features

- Hypertension & weight gain.
- **Truncal obesity**, **moon face**, and accumulation of fat in the posterior neck and back (buffalo hump).
- Proximal limb weakness. (atrophy of type 2 fibers).
- Hyperglycemia, glucosuria, and polydipsia, mimicking diabetes mellitus.
- Easily bruised skin, cutaneous **striae**.
- **Osteoporosis.**
- Increased risk for infections.
- **Hirsutism** and menstrual abnormalities.
- Mental disturbances, including mood swings, depression, and frank psychosis.
- ACTH dependant cushing's syndrome cause skin pigmentation secondary to melanocyte-stimulating activity in the ACTH precursor molecule.



1. Related to treatment.

Causes of Cushing's syndrome

Cushing disease

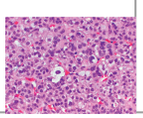
- Primary hypothalamic-pituitary disease associated with hypersecretion of ACTH.
- Accounts for 70% of endogenous cushing syndromes, 4:1 female:male.
- Usually, the pituitary gland contains a ACTH-producing microadenoma.
- Presence of **bilateral nodular** cortical hyperplasia, **secondary** to ACTH.
- ACTH levels are high in urine.

Ectopic ACTH

- Ectopic ACTH secretion by **non pituitary tumors** account for 10% of cases.
- Usually it is a **Small-Cell Carcinoma of the lung**, but could also be carcinoids, medullary carcinoma of the thyroid, or Pancreatic neuroendocrine tumor (PNETs).
- Adrenal glands undergo **bilateral** cortical hyperplasia **secondary** to elevated ACTH.
- High levels of ACTH in urine.

Primary Adrenal neoplasms

- Usually Adrenal adenoma.
- Adrenal carcinoma.
- Rarely **primary** cortical hyperplasia.
- All makeup for 15%-20% of endogenous cushing syndrome.
- Functional and nonfunctional tumors are not morphologically distinct, however, functional neoplasms cause atrophy of adjacent and contralateral adrenal gland.
- ACTH levels are low.

	Adrenal Adenoma	Adrenal Carcinoma
Gross	• Yellow tumors. • Thin, well developed capsule • Weight <30g. 	• Non encapsulated. • Weigh >200-300g.
Microscopy	• Cells similar to those found in zona fasciculata. • Neoplastic cells are vacuolated because of intracytoplasmic lipids. • No mitotic or necrotic activity. 	• Having all anaplastic features.

- Types of primary **cortical hyperplasia:**
  - Macronodular: less than 3 cm in diameter.
  - Micronodular: 1-3 mm and are darkly pigmented.
    - Pigment is believed to be lipofuscin (wear-and-tear pigment).
- High levels of glucocorticoids cause **Crooke hyaline changes:**
  - Granular Basophilic cytoplasm of ACTH secreting cells becomes light basophilic due to **accumulation of intermediate keratin filaments.**

Hyperaldosteronism

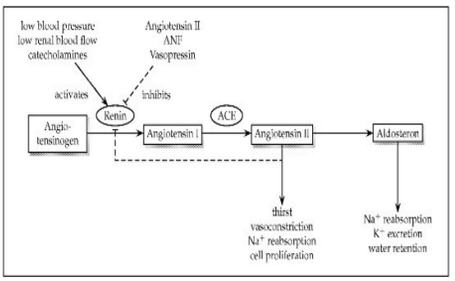
- Chronic excess aldosterone secretion.

Primary Hyperaldosteronism

- **Bilateral idiopathic hyperaldosteronism:**
  - Bilateral nodular hyperplasia of adrenal glands.
  - Most common cause of primary hyperaldosteronism (60% of cases).
  - Some have Mutation in **KCNJ5** gene.
- **Adrenocortical neoplasm:**
  - Aldosterone-producing adenoma.
  - Rarely, Adrenocortical carcinoma.
  - 35% of cases are due to **conn syndrome** a solitary aldosterone-secreting adenoma.
  - Rarely, familial hyperaldosteronism result from overactivity of the aldosterone synthase gene **CYP11B2.**
- Primary aldosteronism results in suppression of the renin-angiotensin system and decrease plasma renin activity.

Secondary Hyperaldosteronism

- Occurs in response to activation of the RAAS system due to:
  - Decreased renal perfusion.
  - Arterial hypovolemia.
  - Pregnancy.



Clinical features

- Secondary hypertension (most common hypertension with identifiable cause).
- Hypernatremia (Aldosterone promotes Na reabsorption)
- **Hypokalemia:** can cause neuromuscular manifestations including weakness, paresthesias, visual disturbance.

Morphology

- **Aldosterone-producing adenoma:** more common in women.

Gross	Microscopy
• Solitary, small (<2cm diameter), well-circumscribed. • Bright yellow on cut surface.	• Uniform size and shape, ocasional nuclear and cellular pleomorphism. • **Spironolactone bodies:** eosinophilic laminated cytoplasmic inclusions, found after treatment with spironolactone.

- Does not suppress ACTH secretion, therefore no atrophic effect.
- **Bilateral idiopathic hyperplasia:** diffuse or focal hyperplasia of cells resembling normal zona glomerulosa.

Hypersecretion of sex steroid

- Hypersecretion of androgens can occur either in:
  - Adrenocortical neoplasms, virilizing[1] neoplasm are more likely to be a carcinoma.
  - **Congenital Adrenal Hyperplasia (CAH):**
    - Autosomal recessive disorders.
    - Defect in steroid biosynthesis: usually in cortisol synthesis.
    - Most common is deficiency in **21-Hydroxylase.**
    - Reduced cortisol increases ACTH secretion which increases synthesis of androgens.
    - Androgens have virilizing effects:
      - In males: precocious puberty.
      - In female: masculinization: ambiguous genitalia, oligomenorrhea, hirsutism.

Adrenocortical insufficiency..

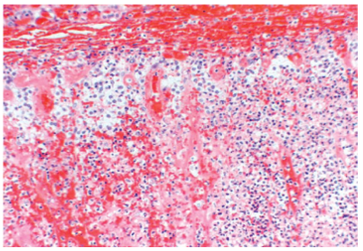
Causes:

- **Primary hypoadrenalism** (adrenal disease): acute (crisis) or chronic (**addison disease**).
- **Secondary hypoadrenalism:** decreased stimulation of adrenals due to deficiency of ACTH

Water-Friderichsen syndrome:

- Bilateral Adrenal **hemorrhage** in **infants** with sepsis, resulting in acute adrenal insufficiency (acute cause).
- Associated with **Neisseria meningitidis septicemia**
- Can also be due to:
  - Pseudomonas spp.
  - Pneumococci.
  - H. influenza.
- **Pathogenesis:**
  Endotoxin-induced vascular injury in vessels supplying adrenal glands with disseminated intravascular coagulation (DIC).
- **Morphology:** autopsy shows
  - Grossly hemorrhagic and shrunken
  - Little residual cortical architecture can be observed

Acute
Water-Friderichsen syndrome
Sudden withdrawal of long-term corticosteroid therapy
Stress in patients with underlying chronic adrenal insufficiency
Chronic
Autoimmune adrenalitis (60%–70% of cases in developed countries)—includes APS1 (AIRE mutations) and APS2 (polygenic)
Infections: Tuberculosis, Acquired immunodeficiency syndrome (AIDS), Fungal infections.
Hemochromatosis
Sarcoidosis
Systemic amyloidosis
Metastatic disease



1- causing masculin biological developments caused mostly by androgens

Addison's disease

- uncommon disorder resulting from **progressive destruction** of the adrenal cortex causing chronic adrenocortical insufficiency.

Causes: 90% are due to one of four causes

- **Autoimmune adrenalitis** (most common cause): autoimmune destruction of steroid-producing cells, and autoantibodies
- **Infection:** tuberculosis and fungal
- **AIDS:** Acquired immune deficiency syndrome
- **Metastatic neoplasm**: Carcinomas of the lung and breast are the source of a majority of metastases in the adrenals

Morphology

- **Primary autoimmune adrenalitis:**
  - **Gross:** shrunken glands hard to differentiate from suprarenal adipose tissue.
  - **Histology:**
    - Scattered residual cortical cells in a collapsed network of connective tissue
    - Lymphoid infiltrate in cortex, *may reach the medulla.*

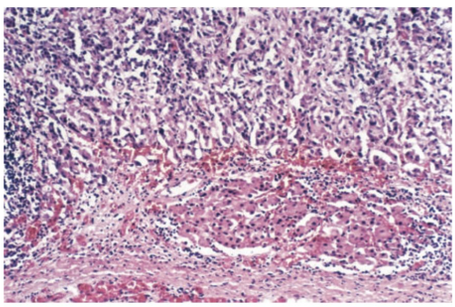


Fig. 20.41 Autoimmune adrenalitis. In addition to loss of all but a subcapsular rim of cortical cells, there is an extensive mononuclear cell infiltrate.

- **Tuberculosis or fungal disease:**
  - **Histology:** adrenal architecture may be effaced by a granulomatous inflammatory reaction identical to that encountered in other sites of infection**.**

Clinical features

- **GIT disturbances:** anorexia, nausea, vomiting, weight loss, diarrhea.
- Hyperpigmentation: due to increased ACTH precursor
- **Decrease Aldosterone:** hyperkalemia[2], hyponatremia, volume depletion and hypotension.
- **Hypoglycemia**
- **Secondary hypoadrenalism:** is characterized by deficient cortisol and androgen output but normal or near-normal aldosterone synthesis.

Complications

- Stress[1] in affected patients leads to acute adrenal crisis
  - Leading to vomiting, abdominal pain, hypotension, and vascular collapse
  - Coma or death can follow if corticosteroids are not replaced

1- infection, trauma, or surgery

2- hyperkalemia is not seen in secondary Adrenocortical insufficiency due to intact RAAS

Adrenocortical neoplasms

- Neoplasms could be functional or non-functional, which could be differentiated based on clinical evaluation, and measurement of hormone or metabolite.

Cortical Adenoma

- Usually non-functional and found incidentally at autopsy or on imaging for unrelated cause.
- If functional, however, could most likely be associated with hyperaldosteronism or cushing syndrome.

Gross morphology:

- On cut surface: yellow or yellow-brown, due to presence of fat in neoplastic cells.
- Small, 1-2 cm in diameter.

Microscopic:

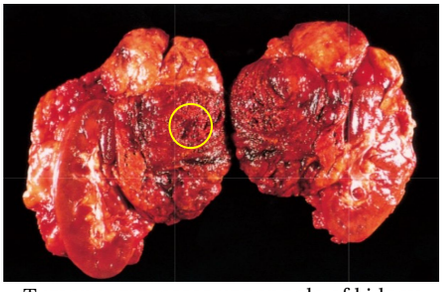
- Small nuclei, some degree of pleomorphism even in benign (endocrine atypia).
- Cytoplasm range from eosinophilic to vacuolated; depending on lipid content.
- Mitotic activity rarely seen.

Adrenocortical Carcinoma

- Rare, could occur at any age, even childhood.
- Two rare inherited causes:
  - Li-Fraumeni syndrome.
  - Beckwith-Wiedemann syndrome.

Gross morphology:

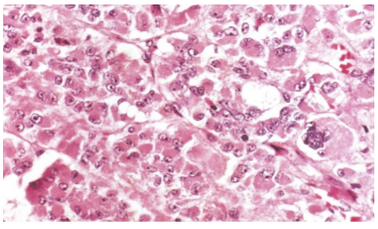
- **Large** invasive lesions that take over normal gland tissue.
- **Cut surface:** variegated[1], poorly demarcated lesions showing
  - Hemorrhage
  - necrosis
  - Cystic change



Tumor compresses upper pole of kidney

Microscopic:

- Anaplastic cells



1- Showing different colours.

Pheochromocytoma

- Neoplasms of **chromaffin cells**, which release catecholamines, these tumors could also secrete other steroids or peptides.
- Surgically correctable forms of hypertension، which could be fatal if left unrecognized.

Rule of tens:

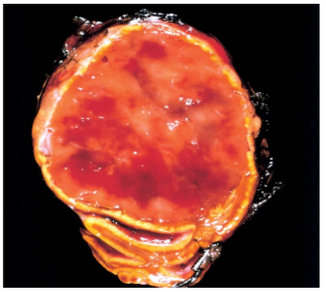
- 10% of pheochromocytomas are extra adrenal (paragangliomas)
- 10% of adrenal pheochromocytomas are bilateral (50% in familial)
- 10% of adrenal pheochromocytomas are malignant
- 10% of adrenal pheochromocytomas are not associated with hypertension
- 10% arise in association with **MEN-2A** and **MEN-2B**

Genetics:

- 25% of individuals with pheochromocytomas and paragangliomas harbor a germ line mutation in one of at least six known genes:
  - RET which causes type 2 MEN syndromes including:
    - NF1 causing type 1 neurofibromatosis
    - VHL causing von Hippel-Lindau disease: Inherited disorder characterized by the formation of tumors and fluid-filled sacs (cysts) in many different parts of the body

Gross

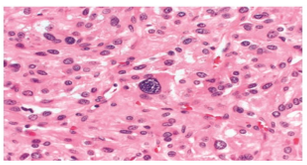
- Range from small circumscribed to large masses weighing several kilograms
  - **Small**: yellow, well-defined, compress adjacent tissue
  - **Large:** hemorrhagic, necrotic, cystic

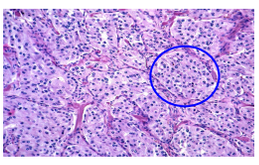


Comma-shaped residual adrenal gland

Microscopy

- Polygonal to spindle-shaped chromaffin cells
- Vascular network form small nests, or **Zellballen**.
- Cytoplasm: fine granular appearance (electron dense)
- Nuclei is pleomorphic
- Capsular and vascular invasion could be seen in benign
- Presence of mitotic figures could also be seen in benign
- Malignancy in pheochromocytomas is diagnosed by the presence of **metastases.**
  - To lymph node.
  - Liver, lung, and bone.





Clinical Features

- **Hypertension**, predominantly
- tachycardia, palpitations, headache, sweating, tremor, and a sense of apprehension.
- risk of myocardial ischemia, heart failure, renal injury, and stroke
- myocardial irritability and ventricular arrhythmia, leading to cardiac death
- **Diagnosis:** demonstration of increased urinary excretion of free catecholamines and their metabolites, such as **vanillylmandelic acid** and **metanephrines**

Summary

Hyperadrenalism	
Cushing's syndrome	**-** exogenous: most common - endogenous: ACTH dependant (cushing's disease, SSC lung), or ACTH independent **Clinical features:** central obesity, moonface, purple striae, buffalo humps, osteoporosis, hyperglycemia, and hirsutism **Morphology:** cortical hyperplasia in ACTH dependant, cortical Atrophy in exogenous and ACTH independent
hyperaldosteronism	**Primary hyperaldosteronism:** idiopathic(KCNJ5 mutation) or adenoma (conn's disease) **Secondary:** RAAS activation by: renal hypoperfusion, pregnancy, hypovolemia **Clinical features:** hypertension, hypernatremia, hypokalemia, leading to weakness and visual disturbance
Hypersecretion of androgens	Hypersecretion due to neoplasm or congenital acquired hyperplasia (21-hydroxylase deficiency) Androgens have virilizing effects: - In **males**: precocious puberty - In **female**: masculinization: ambiguous genitalia, oligomenorrhea, hirsutism
Adrenal insufficiency	
Water-Friderichsen syndrome	Bilateral adrenal hemorrhage due to infectious with **N. meningitidis or other** **Pathogenesis:** endotoxin mediated vascular injury of vessels supplying the glands causing DIC **Morphology:** adrenal gland hemorrhagic and shrunken
Addison's disease	Progressive destruction of adrenal cortex **Causes:** autoimmune, infection, AIDs, Tuberculosis **Gross:** shrunken gland **microscopy:** scattered residual cortical cells **Clinical features:** GIT disturbance, decrease aldosterone, hypoglycemia, - acute adrenal crisis could lead to vascular collapse, coma or death
Adrenal neoplasms	
Cortical Adenoma	- functional could most likely be associated with hyperaldosteronism or cushing syndrome **Gross:** yellow of brown-yellow **Microscopy:** some pleomorphism, cytoplasm eosinophilic or granular, mitosis
Adrenocortical carcinoma	Inherited causes: Li-Fraumeni syndrome, and Beckeith-wiedemann **Gross:** largely invasive, hemorrhage, necrosis **microscopy:** Anaplasia
pheochromocytoma	Neoplasms of chromaffin cells, release catecholamines Arise in association with MEN 2a and 2b **Microscopy:** Zellballen: small nests of cells, granular cytoplasm, Malignancy is based on metastasis **Clinical Features:** Hypertension, tachycardia, tremor, MI, heart failure **Diagnosis:** presence of catecholamines or metabolites (vanillylmandelic acid or metanephrine) in urine.

Quiz

1) A 5-year-boy has developed features that suggest puberty over the past 6 months. On physical examination, the boy has secondary sex characteristics, including pubic hair and enlargement of the penis. Which of the following morphologic features is most likely to be seen in his adrenal glands?
A- Cortical Atrophy
B- Cortical Hyperplasia
C- medullary atrophy
D- medullary hyperplasia

2) A 19-year-old, previously healthy woman collapsed after complaining of a mild sore throat the previous day. On examination she is hypotensive and febrile with purpuric skin lesions. Her peripheral blood smear shows schistocytes. Imaging studies show her adrenal glands are enlarged, and there are extensive bilateral cortical hemorrhages. Infection with which of the following organisms best accounts for these findings?
A- Cytomegalovirus
B- mycobacterium tuberculosis
C- Neisseria meningitidis
D- Streptococcus pneumonia

3) A 37-year-old woman states that, although most of the time she feels fine, she has had episodes of palpitations, tachycardia, tremor, diaphoresis, and headache over the past 3 months. When her symptoms are worse, her blood pressure is measured in the range of 155/90 mm Hg. She collapses suddenly one day and is brought to the hospital, where her ventricular fibrillation is converted successfully to sinus rhythm. On physical examination, there are no remarkable findings. Which of the following laboratory findings is most likely to be reported in this patient?
A- Decreased serum cortisol level
B- Decreased serum glucose level
C- Increased urinary free catecholamines
D- Increased urinary homovanillic acid (HVA) level

4) A 56-year-old woman has had diffuse, dull, constant abdominal pain for the past 2 months. On physical examination no abnormal findings are noted. An abdominal CT scan shows a 3 cm right adrenal mass. The right adrenal is excised and on microscopic examination the mass is composed of cells resembling adrenal cortex. Which of the following features is the most reliable indicator that this mass is malignant?
A- cellular Atypia
B- presence of mitosis
C- invasion
D- size of mass

5) A female infant is born at term to a 41-year-old Yupik woman after an uncomplicated pregnancy. Soon after birth, the neonate develops hypotension. Physical examination shows ambiguous genitalia with a prominent clitoris. Laboratory studies show Na , 131 mmol/L; K , 5.1 mmol/L; Cl, 93 mmol/L; CO2, 18 mmol/L; glucose, 65 mg/dL; creatinine, 0.4 mg/dL; testosterone, 50 mg/dL (normal <30 mg/dL); and cortisol, 2 µg/dL. An abdominal ultrasound scan shows bilaterally enlarged adrenal glands. Which of the following enzyme deficiencies is most likely to be present in this infant?
A- Aromatase
B- 11-Hydroxylase
C- 21-Hydroxylase
D- 17α-Hydroxylase
E- Oxidase

6) Which of the following is the most common cause of Cushing syndrome?
A- Intake of corticoids.
B- Pituitary adenoma.
C- Adrenal adenoma.
D- Ectopic corticotropin syndrome.

7) Virilizing syndromes are caused by which of the following?
A- Increased cortisol.
B- Hyperaldosteronism.
C- Excess androgens.
D- Decreased Cortisol

8- Zellballen refers to which of the following?
A- Small nests of chromaffin cells.
B- Small nests of cortical cells.
C- Small nuclei without pleomorphism.
D- Large nuclei with pleomorphism.

1.B 2.C 3.C 4.C 5.C 6.A 7.C 8.A

Thanks

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Done by the amazing: Khalid..(nothing rhymes with my name)