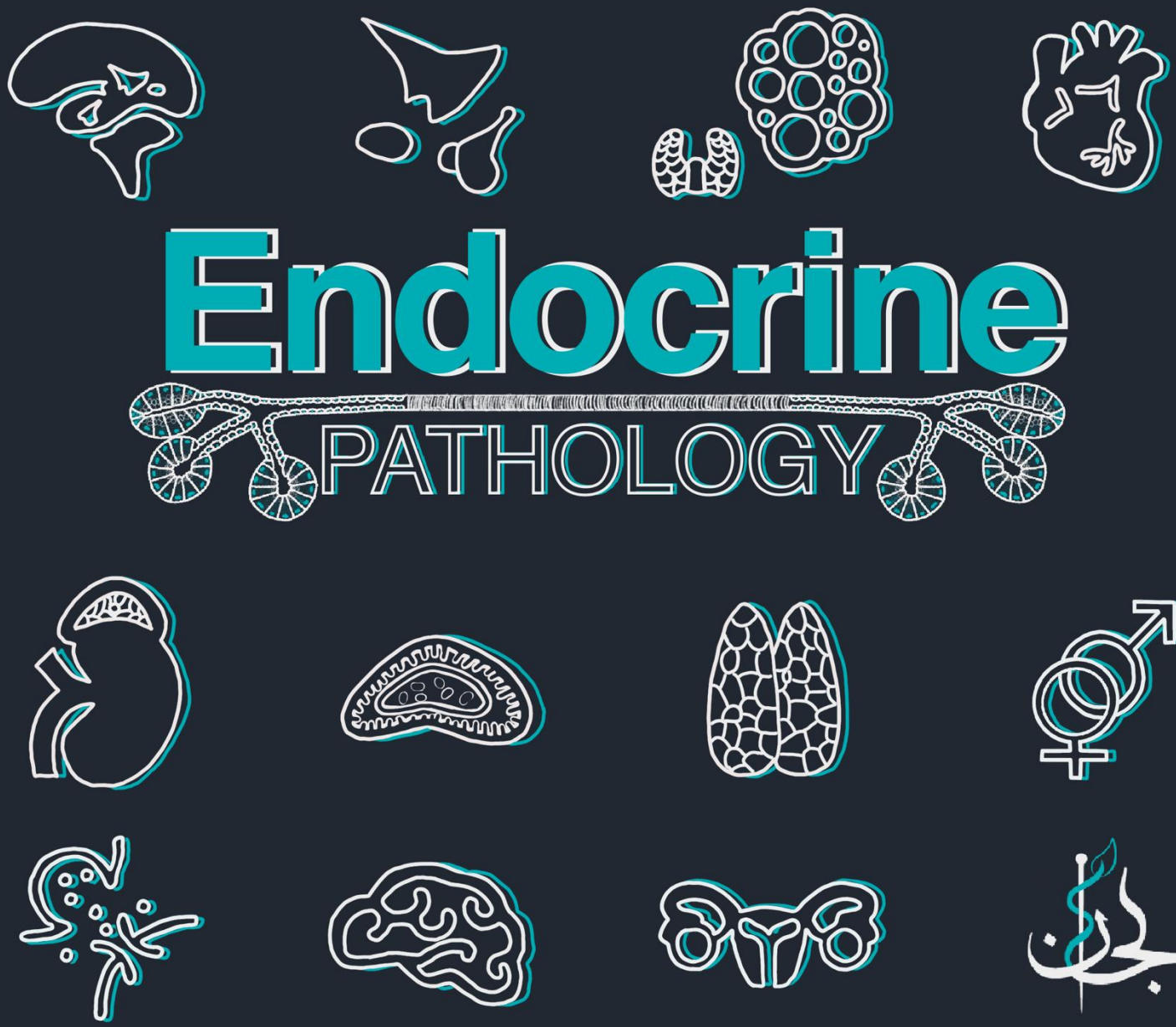

Title: Sheet 2 – Pituitary Adenoma

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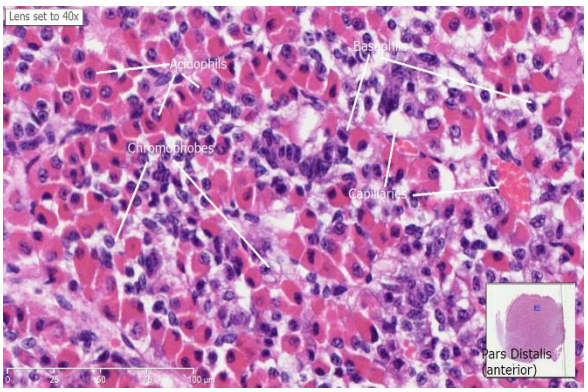
Anterior Pituitary Adenoma

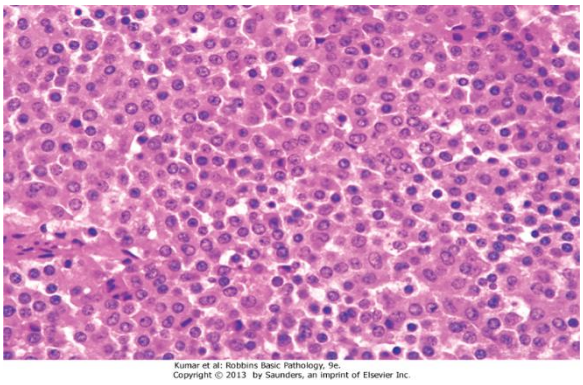
- It's a **benign** tumor of anterior pituitary cells **(0:50-3:25)**
- Could be functional (hormone-producing) or nonfunctional

- **Normal histology** of the anterior pituitary gland: it's composed of 3 cell types → **basophils, acidophils and chromophobes** and the cells are **not monomorphic** like pituitary adenoma

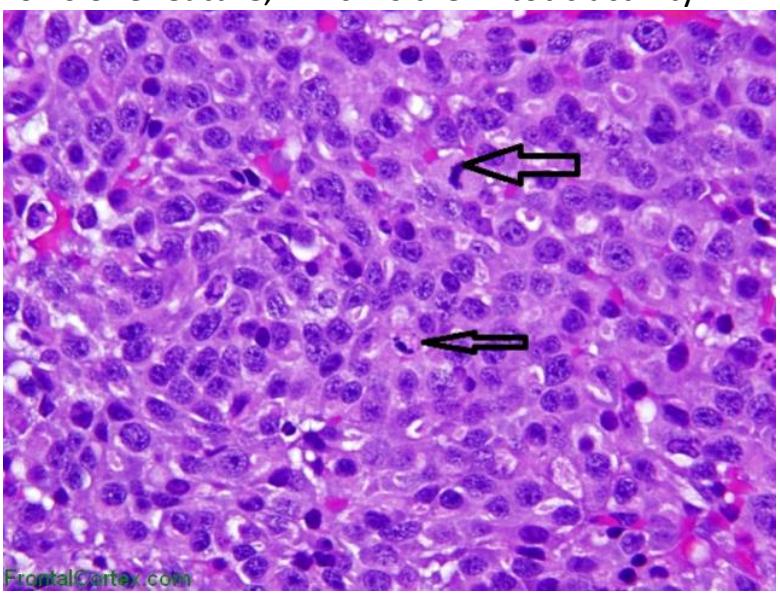


- Histology of pituitary adenoma: **monomorphic** (one cell type → all cells look similar). It's composed of **small, round cuboidal cells** with **small nuclei**, **fine chromatin, and pink to blue cytoplasm**

- Notes
  - ✓ **Cellular monomorphism** and **the absence of a significant reticulin network** distinguish pituitary adenomas from non-neoplastic anterior pituitary parenchyma.
  - ✓ The functional status of the adenoma can't be reliably predicted from its histologic appearance, so we depend on serum level of pituitary hormones



- **Atypical pituitary adenoma**: adenoma that has **TP53 mutations**. It demonstrates brisk **mitotic activity** to reinforce their potential for aggressive behavior.
  This figure only shows one feature, which is the mitotic activity



Types of pituitary adenomas (3:26)

1. **Prolactinomas (most common type… 20%-30%)**

- These are adenomas that produce prolactin → lead to **hyperprolactinemia**
- **Hyperprolactinemia causes**:
  - ✓ Amenorrhea (loss of menses in female) and galactorrhea
  - ✓ Loss of libido (loss the desire for sexual activity) and infertility

  - **Causes of Hyperprolactinemia**:
  - ✓ **Pregnancy and administration of high-dose estrogen therapy**
  - ✓ **Dopamine inhibiting drugs** (e.g. reserpine), because dopamine inhibits secretion of prolactin from the anterior pituitary
  - ✓ **Any mass in the suprasellar compartment** may disturb the normal inhibitory influence of hypothalamus on prolactin secretion (such as dopamine effect), resulting in hyperprolactinemia, a mechanism known as the **stalk effect**.

- Prolactinomas usually are **diagnosed at an earlier stage in women of reproductive age** than in other persons, because they are more likely to have obvious symptoms. For example, a female has amenorrhea. She did some investigating and tests in order know the cause. One of these tests is measurement of serum prolactin level (if it is high, then it's the cause of the amenorrhea).

2. **Growth Hormone-Producing (Somatotroph) Adenomas (5:55)**

- The **second** most common type of functioning pituitary adenoma
- May be **quite large at time of diagnosis** because the clinical manifestations of excessive growth hormone may be subtle

- Clinical manifestations:
  - ✓ Increased growth hormone can cause **Gigantism** or **acromegaly** (depending on the age)
- If a growth hormone-secreting adenoma occurs **before the epiphyses** closes (in children) it causes **gigantism**.
  It's generalized increase in body size, with disproportionately long arms and legs.

- If elevated levels of growth hormone **persist**, or **develop after closure of the epiphyses**, affected persons develop **acromegaly** (in adults), in which:
  1) Growth is most **conspicuous in soft tissues, skin**, and viscera the bones of the face, hands, and feet
  2) **Enlargement of the jaw** results in **its protrusion** with separation of the teeth.
  3) **Enlarged hands and feet** with broad, **sausage-like fingers**

  Extra: sausage-like fingers: characterized by severe inflammation of the finger and toe joints. The puffy nature of the inflammation makes the digits look like sausage.

3. Corticotroph Cell Adenomas (8:21)

- ACTH stimulate adrenal gland to produce cortisol, which has an inhibitory effect on ACTH secretion may be:
  - ✓ Clinically silent
  - ✓ Cause hypercortisolism (increased cortisol), manifested clinically as Cushing syndrome
- One therapy method to cure Cushing syndrome is surgical removal of the adrenal gland. This will lead to loss of feedback inhibition of cortisol on ACTH ,leading to rapid enlargement and more behavior of ACTH producing adenoma and this is called **Nelson syndrome** (Large, clinically aggressive corticotroph cell adenomas).
- This happens because of the metabolic demands and loss of the feedback mechanism.

- ACTH is synthesized as part of a larger pro-hormone substance that includes melanocyte-stimulating hormone (MSH), so if the patient has ACTH producing adenoma, secretion of ACTH will be accompanied by increase secretion of melanocytes stimulating hormone leading to hyperpigmentation of the skin.

4. Gonadotroph LH-producing and FSH-producing adenomas (10:11)

- Can be **difficult to recognize**, because they **secrete hormones inefficiently**, and the secretory products usually do not cause a recognizable clinical syndrome.

❖ **Pituitary carcinomas (10:31)**

- are exceedingly rare and in addition to local extension beyond the sella turcica, these tumors virtually always demonstrate distant metastases.

- As a general rule: **Most endocrine carcinomas are diagnosed depending on behavior (presence of metastases)** and not on histological appearance. i:e under the microscope adenoma and carcinoma can look similar.
  You need to know the clinical information and check if the patient has a metastatic disease in order to call the lesion carcinoma

There's a second type of disease that affect the pituitary, other than mass effect, and it is the hormonal over or under production (Hyperpituitarism, Hypopituitarism)

❖ **Hyperpituitarism** (over production of pituitary hormones) **(11:26)**
- The most common cause is **functional adenoma**
- Other causes:
  - ✓ Hyperplasia and Carcinoma
  - ✓ Secretion of pituitary hormones by nonpituitary tumors.
  - ✓ Hypothalamic disorders

❖ **Hypopituitarism** (decrease production of pituitary hormones) **(13:02)**
- Occurs if there is Loss of at least 75% of anterior pituitary
- Causes:
  - ✓ **Congenital absence** (exceedingly rare)
  - ✓ **Hypothalamic tumors** (associated with posterior pituitary dysfunction).
  - ✓ **Nonfunctioning pituitary adenomas** (Most common), occurs when the adenoma compresses the normal pituitary tissue and affects its function. Also called non secreting and they don't produce clinical manifestations because there will be no hormones. But, by becoming larger in size, the tumor might compress the normal pituitary tissue, causing decrease production of the hormones and therefore, hypopituitarism.

  - ✓ **Ischemic necrosis of the anterior pituitary**, e.g. Sheehan syndrome
  - ✓ **Ablation of the pituitary by surgery**
  - ✓ **Radiation therapy** for head and neck tumors can cause fibrosis of anterior pituitary and hypopituitarism

  - ✓ **Inflammatory lesions** such as sarcoidosis (characterized by the presence of **non-caseating granulomas** that might disrupt the parenchyma of the hypothalamus and pituitary causing hypopituitarism) or tuberculosis (characterized by the presence of **caseating granulomas**)
  - ✓ **Trauma and Metastatic neoplasms** involving the pituitary (the most metastatic tumors are malignant tumor of the lung and the breast. These metastatic tumors might disrupt the pituitary gland causing hypopituitarism)

- **Sheehan syndrome** (or postpartum necrosis of anterior pituitary) **(16:07)**
  - ✓ It is **the most common form** of clinically significant **ischemic necrosis** of the anterior pituitary.
  - ✓ During pregnancy, the anterior pituitary enlarges considerably, because of an increase in the size and number of prolactin-secreting cells

- ✓ This physiologic enlargement isn't accompanied by an increase in blood supply from the low-pressure portal venous system.
- ✓ The enlarged gland is thus vulnerable to ischemic injury, especially in women who experience significant hemorrhage and hypotension during the postpartum period
- ✓ Note: Sheehan syndrome is named after a British pathologist who described the condition

POSTERIOR PITUITARY SYNDROMES (17:20)

- ADH and oxytocin are made in the hypothalamus and then transported via axons to the posterior pituitary for release
  - ✓ ADH acts on the distal tubules and collecting ducts of the kidney to promote free water retention
  - ✓ Oxytocin stimulates contraction of uterine muscles aiding in labor. It is also associated with stimulation of the muscles surrounding the left ferrous ducts of the breast, aiding in lactation.

- Impairment of oxytocin synthesis and release has not been associated with significant clinical abnormalities.
- The clinically important posterior pituitary syndromes involve ADH= vasopressin

❖ **ADH deficiency (18:38)**

- **causes diabetes insipidus (DI)** characterized by **polyuria** (excessive urination) caused by an inability of the kidney to properly resorb water from the urine
- So, patients are thirsty and have **polydipsia** (excessive drinking)
- Diabetes insipidus **can result from several causes**:
  - ✓ **Head trauma, Neoplasms** (in the pituitary and hypothalamus)
  - ✓ **Inflammatory disorders** (sarcoidosis and tuberculosis) and surgical procedures of the hypothalamus and pituitary
  - ✓ The condition may be **idiopathic**.
  - ✓ **Note**: Diabetes insipidus from ADH deficiency is designated as **central DI**, to differentiate it from nephrogenic DI

- **The clinical manifestations** of DI include:
  - ✓ The **excretion of large volumes of dilute urine** with an inappropriately low specific gravity
  - ✓ **Serum sodium and osmolality are increased** as a result of excessive renal loss of free water resulting in thirst and polydipsia
  - ✓ Patients who can drink water generally can compensate for urinary losses, but patients who are bedridden or limited in their ability to obtain water may develop **life threatening dehydration**.

Summary

- **Normal Histology**
  - ✓ 3 cell types (basophils, acidophils and chromophobes) & not monomorphic
- **Adenoma Histology**
  - ✓ Monomorphic
  - ✓ small cuboidal cells with small nuclei, fine chromatin, and pink to blue cytoplasm
- Cellular monomorphism and the absence of a reticulin network distinguish pituitary adenomas from non-neoplastic anterior pituitary
- Atypical pituitary adenoma: has TP53 mutations and high mitotic activity & aggressive

Types of pituitary adenomas

1. **Prolactinomas** (most common type… 20%-30%)

- Hyperprolactinemia causes: Amenorrhea, galactorrhea, Loss of libido and infertility
- Causes of Hyperprolactinemia:
  - ✓ Pregnancy and high-dose estrogen therapy
  - ✓ Dopamine inhibiting drugs (e.g. reserpine)
  - ✓ Any mass in the suprasellar compartment disturb the inhibitory influence of hypothalamus on prolactin secretion (the stalk effect)
- diagnosed at an earlier stage in women of reproductive age (obvious symptoms)

2. **Growth Hormone-Producing (Somatotroph) Adenomas**

- second most common type
- large at time of diagnosis because the clinical manifestations subtle
- Clinical manifestations:
  - ✓ Gigantism: before epiphyses closes (children), increase in body size, long arms and legs
  - ✓ Acromegaly: after closure of the epiphyses (adults), growth is in soft tissues, skin, and viscera & Enlargement of the jaw with separation of the teeth & Enlarged hands, feet with sausage-like fingers

3. **Corticotroph Cell Adenomas**

- Clinically silent or Cause hypercortisolism (Cushing syndrome)
- to cure Cushing syndrome →surgical removal of the adrenal gland →loss of feedback inhibition of cortisol on ACTH →rapid enlargement and of ACTH producing adenoma (Nelson syndrome) → because of the metabolic demands and loss of the feedback mechanism.
- If the patient has ACTH adenoma, it will be accompanied with increase secretion of melanocytes stimulating hormone leading to hyperpigmentation of the skin.

4. **Gonadotroph producing adenomas**

- Difficult to recognize, because they secrete hormones inefficiently, and the secretory products usually do not cause a recognizable clinical syndrome.

Pituitary carcinomas (rare)

- always demonstrate distant metastases.
- under the microscope adenoma and carcinoma→ similar

Hyperpituitarism (cause → functional adenoma)

- Other causes: Hyperplasia, Carcinoma, Secretion of pituitary hormones by nonpituitary tumors, Hypothalamic disorders

Hypopituitarism

- Occurs if there is Loss of at least 75% of anterior pituitary
- Causes:

✓ Congenital absence (rare), Hypothalamic tumors
✓ Nonfunctioning pituitary adenomas (most common, no clinical manifestations, but by becoming larger in size the tumor might compress the normal pituitary tissue causing decrease production of the hormones)
✓ Ischemic necrosis of the anterior pituitary (Sheehan syndrome) & Ablation of the pituitary by surgery
✓ Radiation therapy for head and neck tumors can cause fibrosis of anterior pituitary and hypopituitarism
✓ Inflammatory lesions (sarcoidosis →non-caseating, tuberculosis →caseating granulomas)
✓ Trauma and Metastatic neoplasms involving the pituitary

- **Sheehan syndrome** (postpartum necrosis of ant. pitu)
  - ✓ most common form of ischemic necrosis
  - ✓ During pregnancy →anterior pituitary enlarges because increase in the size and number of prolactin-secreting cells, and it's not accompanied by an increase in blood supply , thus the gland vulnerable to ischemic injury, especially in women who experience hemorrhage and hypotension during the postpartum period

POSTERIOR PITUITARY SYNDROMES

- Impairment of oxytocin synthesis and release has not been associated with significant clinical abnormalities.

ADH deficiency

- causes diabetes insipidus (DI), characterized by polyuria and polydipsia
- Diabetes insipidus can result from several causes:
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