Pathology of Pituitary Adenomas

Classification:

Pituitary adenomas are histopathologically classified by the World Health Organization (WHO) classification according to the hormone content of the tumor cells as assessed by immunohistochemical stains **(Table 1)** ***(Trouillas et al., 2020)***

Table 1: Pathological Classification of Pituitary Adenomas According the 2017 WHO Classification ***(Trouillas et al., 2020)***

Adenoma Types	Morphologic Variants	Pituitary Hormones by Immunohistochemistry	Transcription Factors
Somatrotroph Adenoma			
	Densely granulated adenoma	GH ± PRL, α-subunit	PIT-1
	Sparsely granulated adenoma	GH ± PRL	PIT-1
	Mammosomatotroph adenoma	GH + PRL (in same cells) ± α-subunit	PIT-1, ER-α
	Mixed somatotroph-lactotroph adenoma	GH + PRL (in different cells) ± α-subunit	PIT-1, ER-α
Lactotroph Adenoma			
	Sparsely granulated adenoma	PRL	PIT-1, ER-α
	Densely granulated adenoma	PRL	PIT-1, ER-α
	Acidophilic stem cell adenoma	PRL, GH (focal and variable)	PIT-1, ER-α
Thyrotroph Adenoma		β-TSH, α-subunit	PIT-1

Corticotroph Adenoma			
	Densely granulated adenoma	ACTH	T-PIT
	Sparsely granulated adenoma	ACTH	T-PIT
	Crooke cell adenoma	ACTH	T-PIT
Gonadotroph Adenoma		β-FSH, β-LH, α-subunit (various combinations)	SF-1, ER-α, GATA-2
Null Cell Adenoma		None	None
Plurihormonal Adenomas			
	Pit-1 positive plurihormonal adenoma (previously termed "silent subtype 3 adenoma")	GH, PRL, β-TSH ± α-subunit	PIT-1
	Adenomas with unusual immunohistochemical combinations	Various combinations	

ACTH = adrenocorticotropic hormone; ER-α = estrogen receptor α; FSH = follicle-stimulating hormone; GATA-2 = member of the GATA family of zinc-finger transcriptional regulatory proteins; GH = growth hormone; LH = luteinizing hormone; PIT-1 = pituitary-specific POU-class homeodomain transcription factor 1; PRL = prolactin; SF-1 = steroidogenic factor 1; T-PIT = T-box family member TBX19; TSH = thyroid-stimulating hormone.

Pituitary Adenoma Subtypes:

- **Prolactin-Producing Adenomas**

PRL-secreting adenomas, or prolactinomas, account for nearly 80% of functioning adenomas and about 40–50% of all pituitary adenomas. However, most patients with prolactinomas are treated clinically with dopamine agonists. Therefore, the frequency of prolactinomas in surgical series tends to be smaller ***(Klibanski, 2010).***

Histologically, prolactinomas are composed of medium-sized cells with chromophobic or slightly acidophilic cytoplasm and a central, oval nucleus; small nucleoli can be present. Approximately 10-20% of cases show microcalcifications. Calcifications and amyloid bodies, although frequently seen in prolactinomas, are not pathognomonic of this type of adenoma ***(Lopes et al., 2020)***.

- **GH- secreting Adenomas**

Pituitary adenomas producing GH in excess and clinically associated with gigantism in young patients and acromegaly in adults .The incidence of acromegaly is about 2 to 4 per million with a mean age at presentation of 40–50 years ***(Lodish et al., 2016).***

The WHO definition includes pure GH-producing tumors, mammosomatotroph adenomas, and acidophil stem cell adenomas. Morphologically, the majorities of these tumors are macroadenomas and frequently have suprasellar growth and expansion to the lateral sellar wall. Subtype variants include densely granulated somatotroph adenomas and sparsely granulated somatotroph adenomas ***(Lodish et al., 2016).***

- ***Mixed GH and PRL secreting adenomas***

A large percentage of GH secreting adenomas also secrete PRL. These tumors overall constitute about 8% of pituitary adenomas. In this group of adenomas, three morphologic tumor types can be identified: (1) mixed GH cell/PRL cell adenoma, (2) mammosomatotroph cell adenoma, and (3) acidophilic stem cell adenoma ***(Lopes et al., 2020).***

Morphologically, the tumors are similar to GH-secreting adenomas, with an eosinophilic or chromophobic appearance. Immunostains are demonstrated for both GH and PRL, with varying degrees of staining and distribution ***(Saeger et al., 2007).***

Mammosomatotroph cell adenoma is rare, accounting for fewer than 2% of all pituitary adenomas and about 8% of tumors associated with acromegaly. Acidophilic stem cell adenoma is very rare, representing only a small minority of GH-/PRL-producing tumors ***(Saeger et al., 2007).***

- **Adrenocorticotropic hormone–secreting adenomas**

The ACTH-producing adenomas comprise tumors that are derived from corticotrophs; these tumors comprise about 15% of the clinical cases of pituitary tumors. The majority of ACTH adenomas are very small microadenomas, softer and paler than the normal gland. Microscopically, the typical tumor has a densely granulated basophilic cytoplasm apparent with the classical hematoxylin and eosin stain ***(Lopes et al., 2020).***

- ***TSH-Producing Adenomas***

These tumors are rare and account for about 1% of pituitary adenomas. These tumors in general are macroadenomas and are found to be invasive at the time of surgery. Their color and consistency are generally similar to other pituitary adenomas, but occasionally they can be very firm. Microscopically, the tumors can have either a sinusoidal or a solid pattern. The cells are chromophobic and can have small cytoplasmic granules with PAS stain. Characteristically, the cells have a polygonal or elongated shape ***(Zemskova and Skarulis, 2008).***

- **Gonadotropin-Producing Adenomas**

These comprise the majority of clinically nonfunctioning adenomas. Usually these tumors are macroadenomas with a rich vascular network, frequent necrosis, and hemorrhagic areas. Microscopically, they can have different patterns, but the sinusoidal and papillary pattern is the most common often with perivascular pseudorosettes ***(Lopes et al., 2020).***

- **Plurihormonal Adenomas:**

Plurihormonal adenomas are rare adenomas that have unusual immunoreactivity for multiple pituitary hormones that are not related through the normal cytogenesis and development of the anterior pituitary. Because of their rarity, these tumors do not have a well-characterized clinical presentation ***(Rasul et al., 2014).***

Plurihormonal adenomas do not have specific histopathologic features. This category of adenomas includes the newly described PIT-1 positive plurihormonal adenoma (previously called "silent subtype 3 adenoma"), clinically functioning adenomas such as GH/PRL/TSH-producing adenomas with acromegaly and thyroid dysfunction, and adenomas with unusual combinations of hormones shown by immunostaining that cannot be explained by cytodifferentiation ***(Rasul et al., 2014).***

- **Pituitary Carcinomas**

Primary carcinomas are very rare. The definition of pituitary carcinoma is based on the presence of metastases in other organs including brain or evidence of cerebrospinal fluid dissemination. Microscopically, the tumors have different degrees of high cell density, pleomorphism, necrosis, and invasion, but all of these characteristics can also be found in benign pituitary adenomas ***(Roncaroli et al, 2017).***

- **Null Cell Adenomas**

Under this denomination are the adenomas without any clinical or immunohistochemical evidence of hormonal production. Usually they are macroadenomas and frequently have suprasellar or lateral extension and invasion. Microscopically, the tumors are chromophobic ***(Nishioka and Inoshita, 2018).***

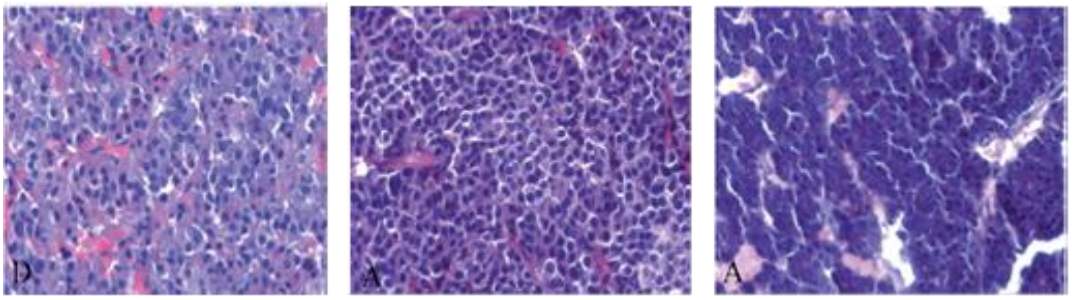

Fig. 25: A: Densely granulated somatotroph pituitary adenoma with acidophilic and densely granulated cytoplasm, B: Prolactinoma composed of cells with chromophobic cytoplasm arranged in a diffuse architectural pattern, C: ACTH-producing pituitary tumor composed of densely granular basophilic cells ***(Nishioka and Inoshita, 2018).***

Ki-67 Antigen and Its Use in Human Cancers

The eukaryotic cell cycle consists of four phases: G1, S, G2, and M. The two main phases are DNA synthesis (S), in which DNA replication takes place, and mitosis (M), in which the replicated genome is divided equally between two new daughter cells. Quiescent cells may again enter the cell cycle from this reversible state in response to growth stimuli; however, the vast majority of cells in the human body exist in a metabolically active state outside the cell cycle called quiescence (G0). Cycling cells are only found regularly in a minority of sites such as bone marrow and epithelial tissues or in abnormal neoplastic tissues.

The Ki-67 antigen is a protein present in the nuclei of cells in the G1, S, and G2 phases of the cell cycle as well as in mitosis. It is not expressed in quiescent or resting cells in the G0 phase, in which many proteins involved in proliferation are degraded ***(Prevedello et al., 2005).***

The presence of Ki-67 antigen is measured by a monoclonal antibody called MIB-1. The MIB-1 immunoreactive nuclear index, also known as the MIB-1 index or the Ki-67 LI, is expressed as a percentage of Ki-67 antigen positive nuclei among total nuclei ***(Prevedello et al., 2005).***

Because the Ki-67 antigen is present in basically all proliferating cells (both normal and tumor); it is an excellent marker for determination of the growth fraction of a given cell population. Because of its special

characteristics, the Ki-67 antigen has been extensively measured to analyze the proliferation rate of many different tumors since its discovery in 1983 ***(Prevedello et al., 2005).***