The role of molecular pathology in the classification and clinicopathologic evaluation of pituitary neoplasms

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Abstract

Pituitary tumors are frequently occurring, most often slowly growing, noninvasive, benign neoplasms. Several types can be distinguished based on their clinical presentation, hormone secretion, growth potential and morphology. The present article describes the pituitary gland and their adenomas based on their morphological characteristics including histologic, immunohistochemical and molecular/genetic profiles. It outlines both the clinically functioning as well as the nonfunctioning adenomas. Many new molecular profiles have been elucidated in pituitary adenomas in the past decade. Some of these new findings emphasize the unique molecular events in different types of pituitary adenomas, although many common pathways have also been reported. The descriptions in this review can be utilized by clinicians, pathologists and researchers as a diagnostic tool to establish diagnosis and classification of various pituitary tumor types.

Keywords ACTH adenoma; gonadotroph adenoma; growth hormone adenoma; molecular genetics; null cell adenoma; pituitary adenoma; prolactin adenoma; TSH adenoma

Anatomy of the pituitary gland

The pituitary gland or "*glandula pituitaria*", as first described by anatomist Andreas Vesalius, lies in the sella turcica, which is a depression in the sphenoid bone. It is protected superiorly by the dura, a dense connective tissue layer lining the sella. Its location is within the vicinity of several structures in the sella and is bilaterally close to the cavernous sinuses, the internal carotid artery, and the oculomotor (CNIII), trochlear (CNIV) and abducens (CNVI) nerves. The optic chiasm lies above the sellar diaphragm and antecedent to the pituitary stalk while on the opposite side, the sphenoid sinus lies in front of the sellar floor.[1,2]

In adults, the normal weight of this bilaterally symmetrical, bean-shaped gland is approximately 0.6 g with dimensions measuring 13 mm (traverse), 10 mm (anteroposterior), and 6 mm (vertical). The pituitary is divided into two distinct lobes: the anterior and posterior lobes. The anterior lobe or adenohypophysis consists of three parts: the pars distalis; pars intermedia and the pars tuberalis. The pars distalis is the largest portion of the pituitary forming approximately 80% of the gland. The posterior lobe or neurohypophysis, connects to the hypothalamus via the hypophysial stalk and forms approximately 20% of the pituitary.

The human pituitary is composed of five distinct cell types that produce six pituitary hormones. They have a unique distribution throughout the gland. The widely accepted perception that the pituitary is composed of three categories of cells, namely, acidophils, basophils and chromophobes is outdated, however, this terminology continues to be widely used and accepted, especially in pathology. The nomenclature which is currently accepted distinguishes the five cell types that produce the pituitary hormones. Of these, growth hormone (GH) cells and prolactin (PRL) cells, belong to the acidophil "cell lines", while the corticotrophs, thyrotrophs and gonadotrophs are part of the basophil "cell lines". The corticotrophs are responsible for the production of adrenocorticotrophic hormone (ACTH), endorphins and β-LPH; the thyrotrophs synthesize thyroid stimulating hormone (TSH); and the gonadotrophs produce follicle stimulating hormone (FSH), luteinizing hormone (LH), and α-subunit. When these cell types are insufficiently granulated, they cannot be stained with acidic or basic dyes and are therefore classified as chromophobic cells. These cells, however, do possess secretory granules and other characteristic structural features at the ultrastructural level when examined by electron microscopy and can therefore be classified as functionally distinct cell types. In the anterior lobe of a normal pituitary gland, the distribution of these cell types is not homogeneous but a general pattern of distribution is perceptible.[1,2]

Growth hormone cells, also known as somatotrophs, make up the majority (~50%) of the adenohypophysial cell population, are mainly located in the lateral wings of the anterior lobe and stain with acid dyes. They are medium-sized, oval or spherical in shape and contain a centrally located round nuclei. The number, distribution and morphology of GH cells are not affected by age, sex or disease but physiologic state may affect their function as it has been shown that GH cells become suppressed during pregnancy. This state is reversible once the production of PRL returns to normal after pregnancy. At the ultrastructural level, GH cells contain well-developed rough endoplasmic reticulum (RER) with prominent Golgi complexes which contain many immature secretory granules. Along with their centrally located nuclei, they have very prominent nucleoli and their well-developed cytoplasm is filled with numerous secretory granules measuring between 250 and 600 nm in size.[1,2]

Prolactin cells, which are also known as lactotrophs, are either acidophilic or chromophobic and account for 15–20% of the adenohypophysial cells. They are scattered irregularly

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throughout the adenohypophysis but are numerous in the posterolateral edges close to the posterior lobe. Two populations of PRL cells have been differentiated: the majority of the cells are sparsely granulated, most prominent in the lateral wings, are elongated or angular, possess long cytoplasmic processes and show a distinctive ring-like PRL immunopositive pattern which corresponds to the globular or ovoid Golgi complex. This cell population is thought to be involved in hormone secretion. The second cell type are polyhedral or elongated, randomly located throughout the gland, and contain cytoplasm that is filled with densely granulated secretory granules. These cells are thought to be resting cells. Ultrastructurally, these two cell populations can be easily distinguished. The densely granulated PRL cells contain large secretory granules measuring between 500 and 700 nm and moderately developed RER with conspicuous Golgi complexes with few immature secretory granules while the sparsely granulated cell population contain smaller secretory granules measuring 150 to m300 nm, abundant RER, prominent Golgi complexes.[1,2]

The frequency of PRL cells in the adenohypophysis varies considerably under certain conditions. There is marked hyperplasia of PRL cells during pregnancy and lactation which leads to an increase in overall weight of the gland. There is no known decrease of number of PRL cells associated with age and cell numbers do not differ significantly between men and nulliparous women.

Corticotroph cells are medium sized, polyhedral or angular with a spherical or ovoid nucleus that make up approximately 15−20% of the adenohypophysial cells.[2] They are known as basophilic cells since they stain positively to basic stains. They also stain positively for periodic acid-Schiff (PAS). Corticotroph cells produce adrenocorticotropic hormone (ACTH) and other fragments of pro-opiomelanocortin (POMC), such as ß-lipotropin (ß-LPH) and endorphins. They are predominately located in the central mucoid wedge but can also be localized in the lateral wings and dispersed amongst other cell types. A unique feature that can be seen with corticotroph cells is their ability to invade into the border between the anterior and posterior lobes where they spread into the posterior lobe. This is known as basophilic invasion and these cells are immunopositive for ACTH.[1] A distinctive morphologic transformation seen in patients with glucocorticoid excess, ectopic ACTH syndrome, Cushing disease or prolonged treatment with pharmacological doses of glucocorticoid hormones is Crooke hyaline change. These cells exhibit a glassy, homogeneous, slightly acidophilic subplasmalemmal ring that displaces the nucleus, organelles and secretory granules to the Golgi complex and to the peripheral portion of the cell. The hyalinized portion does not contain any hormone and is immunonegative for ACTH. Crooke hyaline change is reversible once cortisol levels normalize.[1−3]

Ultrastructural studies show that corticotroph cells contain moderately well-developed RER, prominent Golgi complexes which are spherical or flat in shape, prominent nucleolus which is usually attached to the nuclear membrane and numerous spherical or irregularly shaped secretory granules measuring 300−600 nm that usually line up along the cell membrane.[1,2]

Gonadotroph cells are basophilic cells that show cytoplasmic staining to basic dyes. They constitute approximately 10% of all adenohypophysial cells and produce both follicle stimulating hormone (FSH) and luteinizing hormone (LH) although some gonadotroph cells may contain only FSH or LH. Since it has been demonstrated by immunohistochemistry that both FSH and LH are expressed within the same cell, it is believed that gonadotroph cells originate from the same precursor cell type, which has the ability to produce both FSH and LH. Gonadotroph cells are scattered randomly throughout the lateral wings of the anterior pituitary but can also be found in the mucoid wedge. They have a spherical or ovoid shape, well-developed cytoplasm and a spherical/ovoid nucleus. Ultrastructurally, they are characterized by their medium to large spherical/ovoid cell shape, spherical eccentric nucleus, well-developed RER, prominent Golgi complex, and two distinct populations of secretory granules that range in size from 200 to 300 nm and 300−500 nm.

A separate cell type present in the normal pituitary gland is the thyrotroph cells. These cells produce thyrotroph hormone (TSH) which stimulate thyroid hormones and are the least numerous of the cell types, making up approximately 5% of the adenohypophysial cells. They belong to the basophilic group of cells and are located mainly in the anteromedial portion of the mucoid wedge. They have an angular shape. Electron microscopic study of thyrotroph cells revealed spherical shaped cells with eccentric nuclei, abundant RER, well-developed Golgi complexes, microtubules and secretory granules measuring 100−300 nm and they are usually located along the cell membrane.[1−3]

Pituitary adenomas

Pituitary adenomas (PA) are benign neoplasms arising in adenohypophysial cells. The majority of PAs are slow growing with low cell proliferation rate, however, several PAs are more rapidly growing and have a higher cell proliferation rate. These adenomas are called atypical or aggressive PAs. Adenomas can also be classified as clinically functioning or non-functioning based on whether they secret active hormones or not.

Pituitary carcinomas also occur. They are very rare and can only be diagnosed if distant cerebrospinal and/or systemic metastasis can be documented.[4] In this article, only the benign, slowly growing, clinically functioning or non-functioning PAs and their morphological and immunohistochemical features will be described.

Adenomas producing growth hormone

Adenomas that produce and/or express mainly GH in excess are commonly known as somatotroph adenomas or GH-producing adenomas. They account for approximately 10% of all PAs. This particular adenoma type has been divided into two separate groups based on the number of secretory granules present in the cells. GH-producing adenomas are found mainly in the lateral wings of the anterior pituitary where GH cells are normally found.

Densely granulated GH-producing adenomas (DGGH)

This GH-producing subtype appears to be well differentiated, autonomous and slow growing. They usually show a diffuse growth pattern. Tumors consist of medium sized, round or polyhedral acidophilic cells with granular cytoplasm. Tumor cells contain round nuclei with distinct nucleoli and finely dispersed chromatin. Nuclear pleomorphism has also been

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