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Classification and Pathology of Pituitary Tumors

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Pituitary adenomas originating in adenohypophysial cells represent the most common neoplasms of the sella turcica. The pathologist's goal is the optimal diagnosis and classification of pituitary adenomas. Lack of clinicopathological correlations in the past classification of pituitary adenomas, which was based on the tinctorial properties of adenoma cells, limited the importance of histological diagnosis. Morphologic separation of pituitary cells by electron microscopy provided fundamental knowledge to classify pituitary adenomas. Immunohistochemistry represents the gold standard of the current classification. Combined morphologic and immunohistochemical diagnostic approaches resulted in the clinicopathologic classification of pituitary adenomas. The WHO classification of 2004 is based on morphologic features and takes into consideration findings from imaging procedures and clinical symptoms. Morphologic characterization of pituitary tumors and correlation of the hormone product with hormone secretion provides the clinician with useful information. In addition, the utility of tumor markers offers objective information in managing the patient and predicting responses to specific treatment. The Ki-67 labeling index (LI) is widely used for it correlates with invasiveness and probably prognosis. Adenomas showing increased (>3%) LI and extensive p53 immunoreactivity should be termed "atypical adenomas" suggesting aggressive potential or malignant transformation. Morphologic separation of adenoma from carcinoma is not feasible. The term pituitary carcinoma should be exclusively applied when cerebrospinal and/or systemic metastases are definite.

Key Words: Adenoma; carcinoma; immunohistochemistry; pituitary; ultrastructure.

Introduction

Pituitary tumors are defined as space-occupying lesions of the sella turcica. Among sellar lesions, pituitary adenomas originating from adenohypophysial cells represent the most common neoplasms of this region. The remaining lesions include mesenchymal, neural, or epithelial tumors, metastatic deposits, and other tumor-like growths such as cystic and inflammatory lesions. Therefore, the pathologist has first to recognize and separate adenohypophysial tumors from other neoplasms and tumor-like lesions of the sella turcica, and then to diagnose and classify pituitary adenomas. Certainly, accurate morphologic characterization depends on the availability of adequate material made available by neurosurgeons. The pathologists responsible for handling tissue material have to investigate exhaustively the tissue first to establish the diagnosis and then to use additional material for other purposes. Additional experiments, such as molecular analysis and tissue cultures and cytogenetics, may provide important information; however, the value of these results without correlation with the morphologic diagnosis, remains incomplete.

The present study is focusing on morphologic and immunohistochemical findings of primary adenohypophysial tumors. Other neoplasms and tumor-like lesions involving pituitary and the sella turcica region are presented in Table 1.

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Classification of Pituitary Tumors

In the past, classifications of pituitary adenomas were based on the tinctorial properties of adenoma cells primarily on H&E and histochemical stains *(1)*. The first classification divided adenomas into acidophilic, basophilic, and chromophobic. In nontumorous adenohypophysial gland acidophilic and basophilic cells correlate with somatotroph and corticotroph cells, respectively. However, as a rule, there is no precise correlation of cell-staining properties with adenoma cell type. The classic acidophil adenoma and the classic basophil adenoma associated with acromegaly and Cushing's disease, respectively, represent the only exceptions of this rule. Any other adenoma type, irrespective of the hormone product, may appear chromophobic on H&E sections. As a result, lack of clinicopathological correlations limited the importance of histological diagnosis. Later on, the recognition of distinct morphologic features of adenohypophysial cells by electron microscopy led to the morphologic separation of pituitary cells and classification of pituitary adenomas *(2)*. In addition, immunohistochemistry provided the pathologist with a powerful tool to detect the presence and type of pituitary hormone product. Immunohistochemistry can also reveal structural elements and cytoskel-

Table 1
Tumors and Tumor-like Lesions Other Than Pituitary Adenomas

Neoplasms	**Inflammatory Lesions**
Angioma	Abscess
Angiosarcoma	Acute hypophysitis
Chondroma	Amyloidosis
Chondrosarcoma	Aneurysm
Chordoma	Infections (bacterial, viral, fungal, parasitic)
Choriocarcinoma	Lymphocytic hypophysitis
Choristoma	**Granulomatous Lesions**
Craniopharyngioma	Granulomatous hypophysitis
Fibroma	Tuberculosis
Fibrosarcoma	Sarcoidosis
Esthesioneuroblastoma	Syphilis
Gangliocytoma	Xanthomatous hypophysitis
Ganglioglioma	**Cysts**
Ganglioneuroma	Arachnoid cyst
Germinoma	Dermoid cyst
Glioma	Epidermoid cyst
Glomangioma	Rathke's cleft cyst
Granular cell tumor	**Other**
Hamartoma	Cholosteatoma
Hemangioblastoma	Empty sella syndrome
Hemangioma	Fibrous dysplasia
Hemangiopericytoma	Giant cell granuloma
Leukemia	Giant cell tumor of bone
Lipoma	Hemosiderosis
Lymphoma	Internal carotid artery
Meningioma	Langerhans' cell histiocytosis
Melanoma	Malformations
Metastatic tumors (carcinoma, sarcoma)	Mucocele
Osteoma	Mucopolysaccharidosis
Osteosarcoma	Pituitary hyperplasia
Paraganglioma	
Plasmacytoma	
Postirradiation sarcoma	
Schwannoma	
Teratoma	

eton components, such as mitochondria, and cytokeratin filaments in fibrous bodies and Crooke's hyaline deposits, that only electron microscopy could identify before. Therefore, immunohistochemistry represents the gold standard of all modern diagnostic utilities. Combined morphologic- and immunohistochemical-based diagnostic approaches resulted in the clinicopathologic classification of pituitary adenomas *(3)*. However, electron microscopy remains the only tool to resolve diagnostic problems in some difficult cases. Best practice of pituitary tumor pathology requires optimum classification. Modern diagnosis involves knowledge of current guidelines and application of appropriate techniques for the morphologic characterization of pituitary tumors. Cell differentiation and typing of the hormone product in correlation with hormone secretion provides the clinician with useful information. In addition, the utility of tumor markers offers objective assistance in managing the patient and predicting responses to specific treatment.

The WHO classification of 2004 is based on histologic, histochemical, immunohistochemical, and electron microscopic features and combines them with findings from imaging procedures and clinical signs and symptoms *(4)*.

Epidemiology

Pituitary tumors represent 10–15% of intracranial neoplasms *(5)*. They are more common in adults, comprising 2% of all adenomas in children *(6,7)*. Small incidental tumors frequently occur in autopsy material *(8,9)* and in up to 20% in unselected MRI series *(10,11)*. There are some age and sex differences regarding their incidence. For example, PRL-producing adenomas are the most frequent in adults *(12)* and gonadotroph adenomas in the elderly *(3)*; however, owing to effective pharmaceutical treatment of PRL-producing adenomas, their frequency in surgical series has been significantly decreased *(5)*. Although the reported cure rate of microadenomas is high (65–85%), patients with large PRL-secreting adenomas associated with mass effects, mostly sudden visual disturbances, or resistant to dopamine therapy are usually driven to surgery *(13)*. The substantial majority of pituitary adenomas are single; multiple adenomas occur in less that 1% in surgical and autopsy series *(14, 15)*. From the clinical point of view, it is important to know their existence to explain surgical failure in case one adenoma was removed and the other was left behind *(15)*.

Prognosis and Predictive Factors

Most pituitary adenomas are slowly growing tumors. Therefore, mitoses, if present, are rare and difficult to identify and count. Alternatively, the Ki-67 antigen is widely used by the WHO classification for it correlates with invasiveness and probably prognosis *(4,16)*. The Ki-67 antigen is expressed through all cell cycle phases except for the early G1 phase. The MIB epitope of Ki-67 antigen is highly repetitive and remains stable in formalin-fixed and paraffin-embedded tissues *(17)*. The Ki-67 labeling index (LI) is low, about 1% in most pituitary adenomas (Fig. 1). Adenomas with more than 3% Ki-67 LI may show aggressive clinical course. Some invasive adenomas and carcinomas show extensive immunohistochemical expression of p53 suppressor oncoprotein *(18)*. However, mutations of *p53* suppressor gene have not been detected. According to the recent WHO classification, adenomas showing increased (>3%) LI and extensive immunoreactivity for p53 should be termed "atypical adenomas" to signify their aggressive potential or malignant transformation *(4)*. In our current practice we apply Ki-67 immunostaining to all pituitary adenomas and p53 to tumors with a Ki-67 LI >3%. It has been proposed that atypical tumors and those with Ki-67 LI

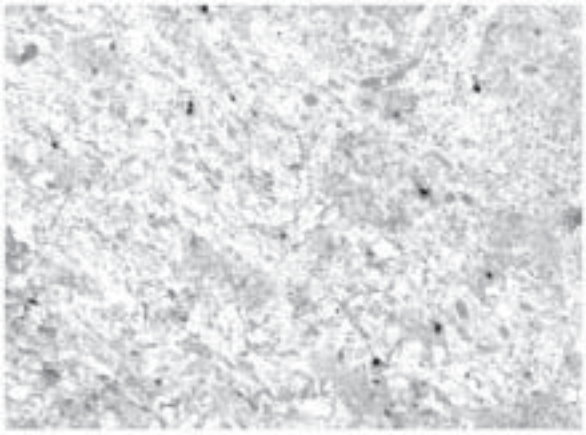

Fig. 1. This GH producing adenoma shows a low, approx 1% labeling index (LI) (Ki-67, clone MIB1, 10×).

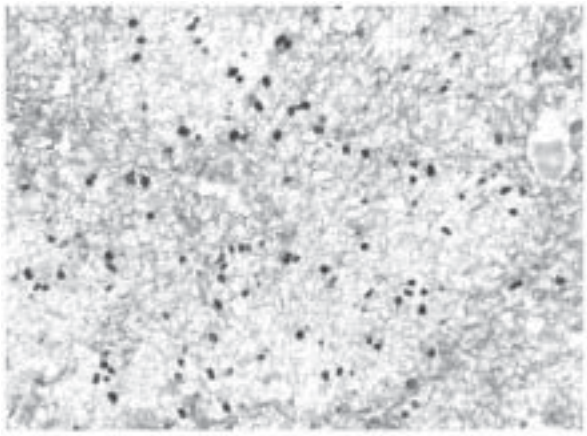

Fig. 2. A high LI estimated at approx 10% in a TSH-producing adenoma is shown [avidin–biotin–peroxidase complex technique (ABC), Ki-67, clone MIB1, 10×].

greater than 10%, irrespective of p53 immunostaining, should be followed-up for early recurrence and presence of metastases (Fig. 2) *(19)*. As a rule, the Ki-67 LI is significantly higher and p53 expression is more consistent in pituitary carcinomas as compared with adenomas *(16)*. Therefore, the Ki-67 represents a predictive factor, which reveals the tumor proliferation rate, thus providing the clinician with valuable information that was not available previously.

GH-Producing Adenomas

These adenomas represent 25–30% of pituitary tumors in surgical material and show no sex predilection. Their lower incidence in clinical series is due to inclusion of medically treated adenomas *(20)*. Most tumors are macroadenomas producing ballooning enlargement of the sella turcica, often with upward and/or lateral extension. They are characterized by GH/IGF-I excess, and are clinically associated with either gigantism or acromegaly, depending on patient's age at onset of the disease. Additional clinical associations

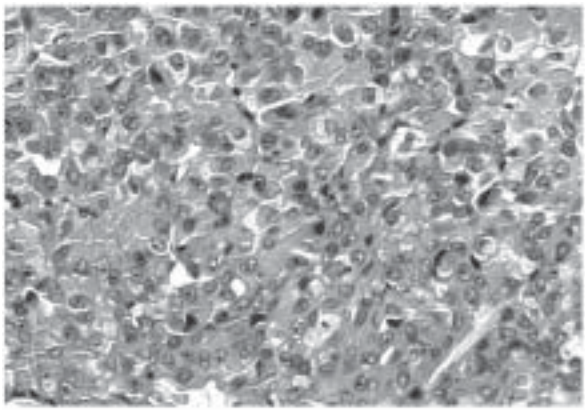

Fig. 3. This densely granulated GH-producing adenoma is composed of polyhedral medium-sized cells with acidophilic cytoplasm and oval nuclei with prominent nucleolus (H&E, 20×).

include mass effects and tumor-induced adenohypophysial hypofunction *(21)*. Mammosomatotroph adenomas represent the most common cause of gigantism, when they occur in young patients. Densely granulated and sparsely granulated somatotroph adenomas represent two variants of solely GH-producing tumors with distinct morphology and immunoprofile and show slight differences regarding their clinical, molecular, and biochemical associations. GH-producing adenomas account for approximately two thirds of double adenomas identified in surgical series *(15)*, but they are very rare among multiple adenomas incidentally found in autopsy material *(22)*.

Densely Granulated Somatotroph Adenomas

This variant corresponds to the classic acidophil adenoma. The tumor cells are similar to nontumorous somatotroph cells. They are large polyhedral with round nuclei, often exhibiting prominent nucleolus (Fig. 3). The cytoplasm contains abundant, large secretory granules and demonstrates strong and diffuse immunoreactivity for GH (Fig. 4). Up to 50% of these tumors show plurihormonal immunophenotype and are also positive for α- and/or β-subunits of TSH, FSH, or LH *(3,22)*.

Sparsely Granulated Somatotroph Adenomas

This variant consists of chromophobic cells lacking similarities to any cell type of the nontumorous adenohypophysial gland. The adenoma cells are smaller with conspicuous nucleolus. The diagnostic feature of this variant is the presence of pale acidophilic, spheroid cytoplasmic inclusions known as fibrous bodies. Adenoma cells containing fibrous bodies show peripheral displacement of the nucleus, often with crescent formation, and may harbor multinucleated or pleomorphic nuclei (Fig. 5). The cytoplasm contains sparse and small secretory granules, thus showing variable immunoreactivity for GH (Fig. 6). The fibrous bodies consist of concentric aggregates of keratin intermediate filaments strongly reactive for low molecular weight cytokeratins, particularly for keratin 8 *(23,24)* (Fig. 7).

Fig. 4. Immunohistochemistry in a densely granulated somatotroph adenoma shows diffuse cytoplasmic reactivity for GH with prominent membranous distribution (ABC, GH, 20×).

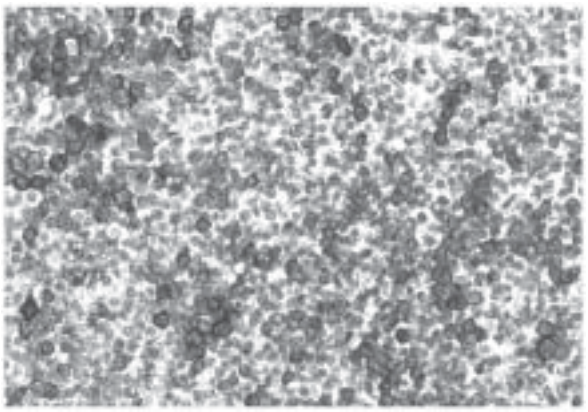

Fig. 6. Heterogeneous immunoreactivity for GH in a sparsely granulated somatotroph adenoma (ABC, GH, 20×).

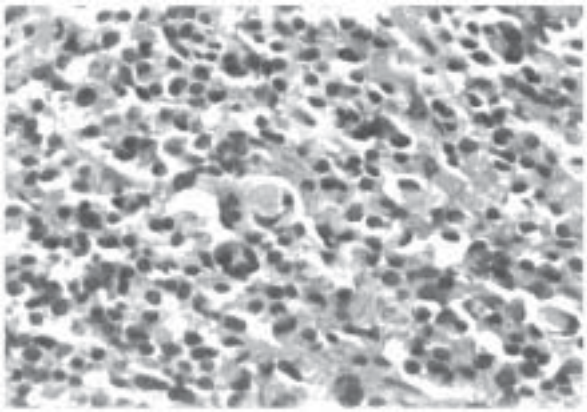

Fig. 5. Sparsely granulated somatotroph adenoma. Some cells include fibrous bodies in the cytoplasm and show peripherally displaced multiple nuclei (H&E, 20×).

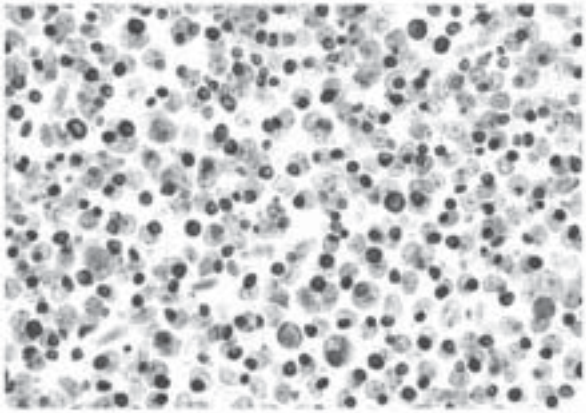

Fig. 7. Keratin 8 reveals size-differing fibrous bodies in many cells of this sparsely granulated somatotroph adenoma (ABC, CAM 5.2, 20×).

Mixed Somatotroph–Lactotroph Adenomas

These uncommon tumors are bimorphous consisting of somatotroph and lactotroph cells. The two different adenoma cell populations are variably admixed and each particular cell type shows separate immunoreactivity for GH and PRL.

Mammosomatotroph Adenomas

These are monomorphous tumors consisting of a single cell type. By histology, the adenoma cells are acidophilic, identical to densely granulated somatotroph adenoma. By immunohistochemistry, GH and PRL reactivities are colocalized in the same cells. By electron microscopy the cells resemble densely granulated somatotrophs of the nontumorous pituitary. In addition, they show misplaced exocytosis, a characteristic feature of PRL-secreting cells *(3,25)*. Some cells may contain small fibrous bodies, which can easily be detected by immunohistochemistry for keratin 8 *(24)*.

Acidophil Stem Cell Adenomas

These unusual monomorphous, slightly acidophilic tumors show nuclear pleomorphism with coarse chromatin and prominent nucleoli. The large cytoplasmic vacuoles corresponding to giant mitochondria, the presence of fibrous bodies immunoreactive for keratin 8 and the misplaced exocytosis represent the key diagnostic features of this adenoma type. Immunoreactivity for PRL is often associated with less pronounced positivity for GH. However, only electron microscopy can establish the diagnosis.

Effect of Somatostatin Agonists

Long-acting somatostatin analogs are widely used to treat mostly GH-producing adenomas, particularly in the case of surgical failure *(26,27)*. These drugs, binding to somatostatin receptors, reduce pituitary GH secretion and plasma IGF-1 levels and suppress tumor-cell proliferation *(27,28)*. Although these drugs do not usually cause a significant reduction of tumor volume, preoperative administration may reduce complications and improve surgical outcome *(29)*.

Morphologic changes include slight increases in the size and number of secretory granules, accumulation of lysosomes, and mild to moderate stromal fibrosis and hyalinization *(26,30)*.

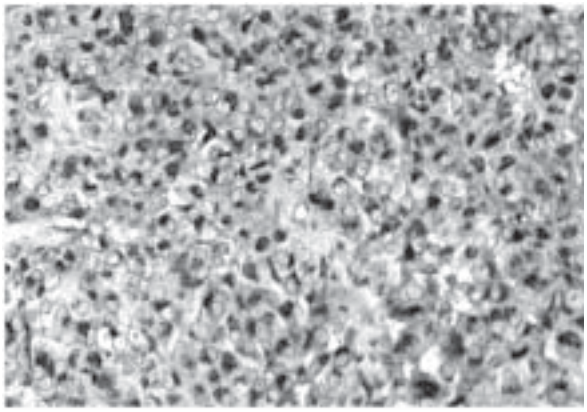

Fig. 8. Sparsely granulated lactotroph adenoma with characteristic paranuclear, dot-like immunoreactivity for PRL (ABC, PRL, 20×).

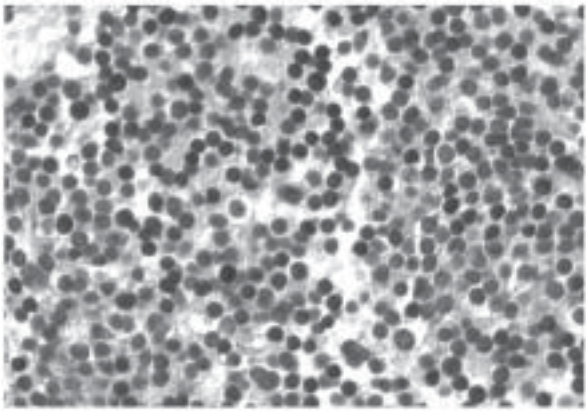

Fig. 9. PRL-producing adenoma treated with dopamine agonists. Note morphologic changes including nuclear hyperchromasia and reduction of nuclear and cytoplasmic volume (H&E, 20×).

PRL-Producing Adenomas

These adenomas are associated with hyperprolactinemia; the serum PRL levels usually correlate with the tumor size. They represent the most common neoplasm of the anterior pituitary in clinical series and in autopsy material *(8, 12)*. Although they were the first among surgical series two decades ago, their frequency has been dramatically decreased after the introduction of the effective dopamine agonist therapy *(5)*.

Owing to clinical manifestation mostly presenting as amenorrhea–galactorrhea, PRL-secreting adenomas are usually microadenomas in females. In contrast, in males they present as macroadenomas in the majority of cases, because of delayed diagnosis due to their modest clinical symptoms, such as decreased libido and sexual impotence *(3)*. PRL-producing tumors show the highest incidence among pituitary adenomas in childhood and adolescence *(6,7)*.

The great majority of PRL-producing tumors correspond to sparsely granulated lactotroph adenomas. By histology, these tumors are chromophobic and contain spheroid nuclei with prominent nucleolus. Psammoma bodies and interstitial amyloid deposits, occasionally seen, are typical for this adenoma type *(3,24)*. The dot-like paranuclear localization of PRL immunoreactivity, the so-called "Golgi pattern," is a characteristic diagnostic feature for PRL production (Fig. 8). Misplaced exocytosis, representing granule extrusion into the extracellular space, is considered an electron microscopic hallmark for PRL secretion *(3,25)*.

Effect of Dopamine Agonists

The morphologic changes of dopamine agonists in PRL-producing adenomas after long-term treatment have been described in detail. Several studies of the last two decades reported dramatic alterations in the majority of treated tumors. By histology, the tumors often appear hypercellular due to significant cell shrinkage. The cells undergo shrinkage with remarkable reduction of the cytoplasmic volume, nuclear hyperchromasia, and increased nuclear/cytoplasmic ratio (Fig. 9). Long-term administration leads to development of extensive perivascular and interstitial fibrosis. Some tumors show reduced immunoreactivity for PRL. Electron microscopy demonstrates marked reduction of RER and Golgi complexes volumes. In some cases, morphologic changes are heterogeneous and some cells remain unaffected. This uneven response to dopamine agonist therapy may be attributed to heterogeneous expression of D_2 receptors among adenoma cells. These effects appear reversible after discontinuation of therapy, although some adenomas do not regrow *(3)*.

Recent studies have documented the occurrence of apoptosis in PRL-producing tumors and the morphologic changes of apoptotic events have recently been described in detail by histology and electron microscopy *(31)*. In some studies, the apoptotic and Ki-67 proliferation indices have been found to differ between PRL producing adenomas treated with dopamine agonists and untreated tumors. Divergent results reported in other studies may be explained by differences in type of drug used, daily dose, duration of treatment, and degree of responsiveness of cells to dopamine agonists *(32)*.

ACTH-Producing Adenomas

The ACTH-producing adenoma, which is clinically manifested as Cushing's syndrome, derives from the anterior pituitary corticotrophs that synthesize several additional proopiomelanocortin cleaved peptides including β-LPH and β-endorphin *(33)*. Corticotroph adenomas represent the approx 10% of pituitary tumors *(4)*. Corticotroph adenomas show female predilection with an 8:1 female to male ratio *(34)* and they are rare in childhood *(6)*. The substantial majority of adenomas associated with Cushing disease measure less that 1 mm; pituitary MRI reveals a microadenoma in about 80% of cases. However, microadenomas less that 4 mm are not demonstrated by imaging procedures even though there is clinical evidence of adenoma *(35,36)*. In addition, histology cannot identify a small subset of tumors

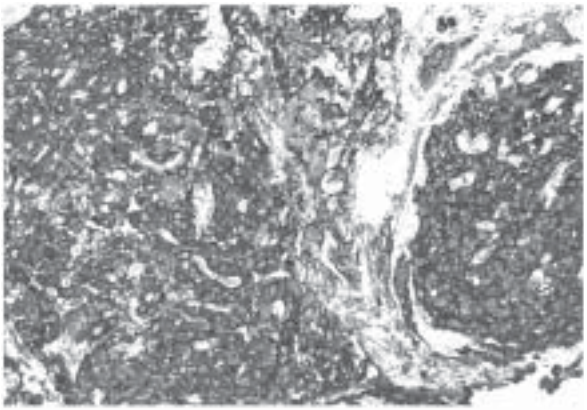

Fig. 10. This corticotroph adenoma shows diffuse cytoplasmic immunoreactivity for ACTH (ABC, ACTH, 10×).

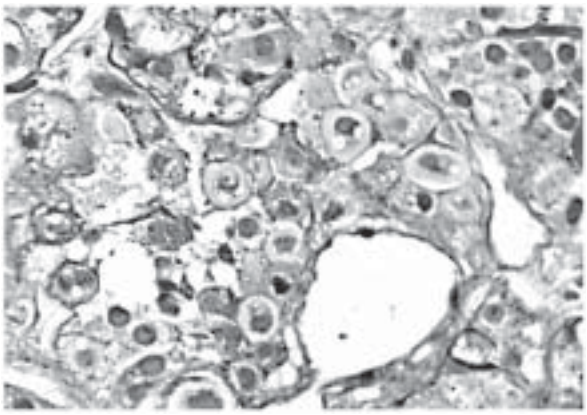

Fig. 11. Crooke's change. Several nontumorous corticotrophs show amorphous hyaline deposits (PAS stain, 20×).

due to loss during surgery or during sectioning of the tissue specimen.

Histology shows a typical basophilic adenoma consisting of monomorphous round cells with plump cytoplasm and ovoid nuclei with conspicuous nucleolus. The adenoma cells are often strongly PAS positive, although adenoma cells containing abundant keratin intermediate filaments may be weakly PAS positive. Some tumors may show nuclear pleomorphism and apoptotic figures. Crooke's hyaline change, corresponding to accumulated cytokeratin intermediate filaments in the cytoplasm of non-neoplastic corticotrophs, is commonly present. By immunohistochemistry ACTH is positive (Fig. 10). In some cases, ACTH reactivity is less pronounced due to the presence of abundant cytokeratin filaments (Fig. 11). Crooke's adenomas represent ACTH-producing tumors with massive hyaline deposits in adenoma cells. By electron microscopy, depending on the size and number of the secretory granules, corticotroph adenomas can be divided in densely granulated and sparsely granulated.

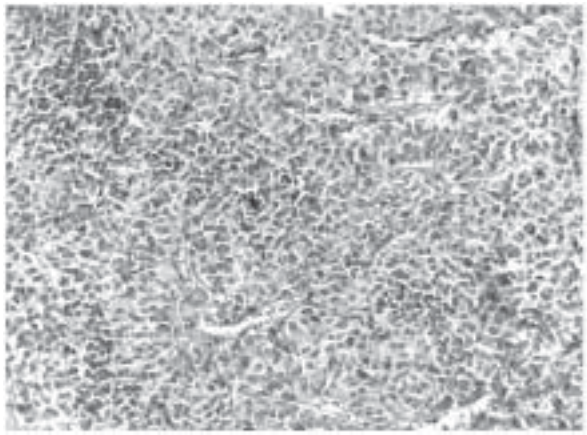

Fig. 12. Chromophobic TSH-producing adenoma composed of round to polyhedral cells, with tendency for perisinusoidal arrangement (H&E, 10×).

Silent Corticotroph Adenomas

Silent subtype 1 adenomas are identical by histology, immunohistochemistry, and electron microscopy to functioning ACTH adenomas, but are clinically nonfunctioning. Crooke's hyaline change is not detectable in non-tumorous corticotroph cells of the adjacent adenohypophysial parenchyma *(33)*. Silent subtype 2 adenomas are chromophobic and contain sparse and smaller secretory granules *(33,37)*.

TSH-Producing Adenomas

This type of adenoma is rare representing approx 1% among pituitary adenomas. Most tumors are macroadenomas and show female predilection *(38,39)*. Thyrotroph adenomas mostly secrete TSH in excess and present with a goiter and hyperthyroidism. Misdiagnosed patients treated with surgery or radioiodine often exhibit progressive growth and invasiveness of the thyrotroph adenoma.

By histology the chromophobic adenoma cells are polyhedral or polar and show varying degrees of nuclear pleomorphism (Fig. 12). The PAS stain reveals positive tiny cytoplasmic granules corresponding to lysosomes. Immunohistochemistry is positive for α- and β-TSH subunits. Immunohistochemistry and electron microscopy highlight the elongated cytoplasmic processes of the tumor cells (Fig. 13). The small secretory granules are arranged along the cytoplasmic membrane and accumulate in the cell process.

Gonadotropin-Producing Adenomas

Gonadotropin-producing adenoma is composed of gonadotroph cells producing pituitary gonadotropins, i.e., FSH and LH. The reason that these tumors are usually unassociated with apparent endocrinological symptoms in conjunction with lack of sensitivity of the immunohistochemical techniques used in the past, led to the conclusion that gonadotropin-producing adenomas were rare. These tumors were included in a heterogeneous category originally termed "null

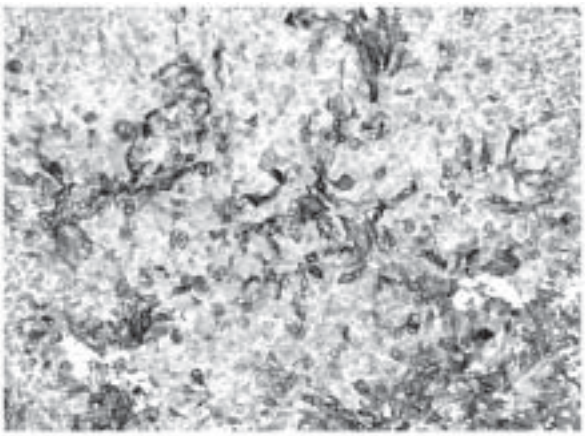

Fig. 13. Immunostain for β-TSH discloses polyhedral adenoma cells with attenuated cytoplasmic processes (ABC, β-TSH, 10×).

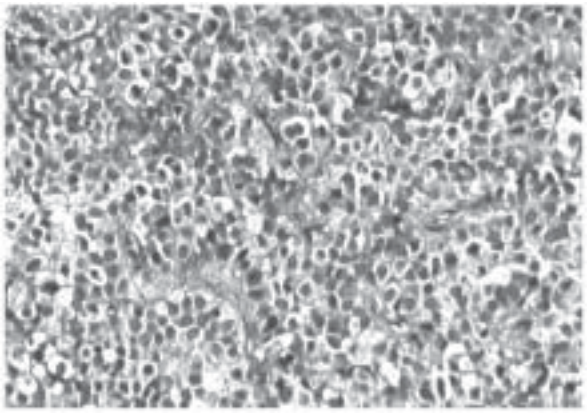

Fig. 14. Chromophobic gonadotroph adenoma composed of round cells. The nuclei are regular and some of them have conspicuous nucleolus (H&E, 20×).

cell" adenomas *(40)*. Currently, gonadotropin-producing adenomas represent the majority of nonfunctioning pituitary adenomas and some are incidentally identified by MRI or at autopsy. They are mostly diagnosed late as large tumors, often with upward grow, compressing the optic chiasm or invading the surrounding structures.

Typically, gonadotropin-producing adenomas consist of small round to middle-sized polar cells, often with perisinusoidal pattern with elongated cytoplasmic processes forming characteristic pseudorosettes or pseudopapillae. They show uniform spherical to slightly ovoid nuclei with scant nucleolus (Fig. 14). The cytoplasm is often granular, acidophilic due to oncocytic transformation *(41,42)*. The PAS stain is negative, although some adenoma cells may show PAS-positive granules corresponding to lysosomes.

The typical immunophenotype includes one or more of β-FSH, β-LH, and α-glycoprotein hormone subunits. The distribution of immunoreactivity is heterogeneous, mostly focal and immunoreactivities for β-FSH, and β-LH are not necessarily confined to the same cells. Immunohistochemistry demonstrates the cytoplasmic configuration and highlights the cytoplasmic processes where the secretory granules accumulate (Fig. 15). Gonadotropin producing adenomas are also immunoreactive for synaptophysin, chromogranin A, and, according to recent studies, for inhibin and activin subunits *(43)* and the transcription factor steroidogenic factor 1 (SF1) *(44)*.

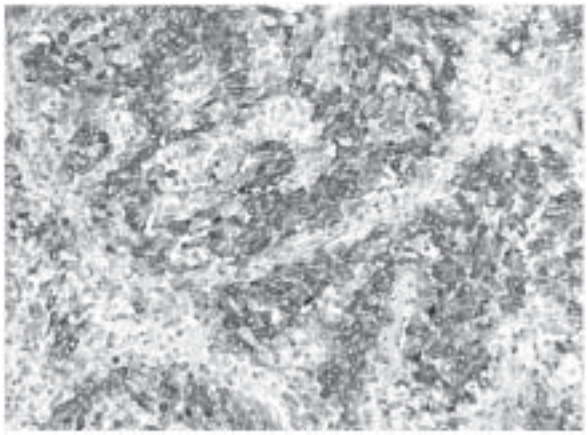

Fig. 15. Immunostain for β-LH reveals the polar shape of adenoma cells and highlights the elongated cytoplasmic processes (ABC, β-LH, 10×).

Electron microscopy shows cells with polar cells and reveals tiny secretory granules lining-up along cytoplasmic membranes, in addition to those accumulating in the cytoplasmic processes, a feature also known as "glycoprotein hormone differentiation" *(42)*. In females, the Golgi apparatus shows characteristic vesicular, "honeycomb-like" transformation *(45,46)*. This unique abnormality represents a diagnostic feature, particularly in tumors with inconclusive or negative immunoreactivity for gonadotropin hormones. Gonadotroph adenomas often show high accumulation of mitochondria in the cytoplasm, known as oncocytic transformation.

Null Cell Adenomas

By definition, null cell adenomas are tumors that have no immunohistochemical or ultrastructural markers to disclose specific adenohypophysial cell differentiation *(40)*. However, some tumors may contain few, scattered cells immunoreactive for pituitary gonadotropins. They occur in elderly patients mostly over 60-yr *(41)* and their incidence is gradually decreasing due to the improved sensitivity of immunohistochemical techniques *(42)*. In most cases, the tumors are large, presenting with mass effects, due to compression of the adjacent structures, mild hyperprolactinemia, due to stalk section effect, and hypopituitarism *(47)*.

By histology, null cell adenomas are typically chromophobic, with pseudopapillary pattern of growth, often with pseudorosette formation. They contain round nucleoli with focally conspicuous nucleolus and no marked nuclear pleomorphism or mitotic activity. Despite the scarcity of immunoreactivity for gonadotropins, molecular techniques reveal

their presence *(48,49)*. In addition, these tumors are immunoreactive for chromogranin A and synaptophysin.

Electron microscopy demonstrates poorly developed cytoplasmic membranous organelles including scattered arrays of rough endoplasmic reticulum and Golgi apparatus saccules. The secretory granules are sparse and small measuring 100–250 nm. Increased number and volume density of cytoplasmic mitochondria leading to oncocytic transformation is also frequent.

It seems that null cell adenomas and oncocytomas belong to the same entity with gonadotroph adenomas *(42)*. However, other nonfunctioning adenomas, such as silent GH-producing and ACTH-producing adenomas and silent subtype 3 adenomas, should be differentiated for they may show higher proliferation rate and recur more frequently than null cell adenomas *(4,37,49)*.

Plurihormonal Adenomas

They represent unusual adenomas composed of cells that are immunoreactive for more than one pituitary hormone and cannot be explained by normal adenohypophysial cytodifferentiation. Adenomas immunoreactive for GH and PRL or immunopositive for FSH and LH are not considered plurihormonal. The pathologists should be aware that the presence of a few scattered cells showing immunoreactivities for various pituitary hormones may correspond to trapped nontumorous adenohypophysial cells. In plurihormonal adenomas the most frequent combinations include GH, PRL, and one or more glycoprotein hormone subunits (β-TSH, β-FSH, β-LH, and α-SU) *(22)*. The unusual silent subtype 3 adenoma, representing the only plurihormonal tumor type with a characteristic ultrastructural profile, is often immunoreactive for PRL and TSH *(37,49)*. Diagnosis of silent subtype 3 adenoma, which is based on electron microscopy, is very important because these rare tumors exhibit aggressive behavior and poor prognosis; they are highly infiltrative, showing rapid growth and high recurrence rate *(4,37,49)*.

Pituitary Carcinomas

Morphologic separation of pituitary adenoma from a carcinoma is not possible. The term pituitary carcinoma is exclusively applied when cerebrospinal and/or systemic metastases are definite *(4)*. Primary pituitary carcinomas are very rare representing approx 0.2% in surgical series. Pituitary carcinomas affect adults with no age or sex preponderance. They are associated with poor prognosis; the mean survival rate is 8 yr for approx 80% of patients with documented metastases. Two thirds of pituitary carcinomas are endocrinologically functional primarily producing PRL or ACTH. Metastases of pituitary carcinomas include dissemination throughout the subarachnoid space and lymphatics. Hematogenous dissemination has been reported only in a few cases, primarily of ACTH-producing carcinomas *(19,50)*.

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