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Pathology of pituitary tumors

Naoko Sanno, MD, PhD[a,*], Akira Teramoto, MD, DMSc[a], R. Yoshiyuki Osamura, MD, PhD[b], Eva Horvath, PhD[c], Kalman Kovacs, MD, PhD[c], Ricardo V. Lloyd, MD, PhD[d], Bernd W. Scheithauer, MD, PhD[e]

[a]*Department of Neurosurgery, Nippon Medical School, 1-7-1 Nagayama Tama, Tokyo 206–8512, Japan*
[b]*Department of Pathology, Tokai University School of Medicine, Isehara, Japan*
[c]*Department of Pathology, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada*
[d]*Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA*
[e]*Department of Pathology, Mayo Clinic, Rochester, MN, USA*

Pituitary adenomas are benign neoplasms originating in adenohypophysial cells. They represent the most common neoplasm of the sellar region, comprising approximately 15% of all primary intracranial tumors [1–3]. Depending on the studies of unselected adult autopsy material, their frequency as an incidental finding varies between 5% and 20% [1,4].

In the first part of this article, the immunohistochemistry of nontumorous human adenohypophysis is briefly summarized. In the second part, the classification of pituitary tumors is discussed, followed by the immunohistochemical and electron microscopic findings of pituitary adenomas and pituitary carcinomas.

Pathologic findings of nontumorous adenohypophysis

The adenohypophysis consists of five different secretory cell types (somatotrophs, lactotrophs, corticotrophs, thyrotrophs, and gonadotrophs) and is distinguished functionally by its capacity to secrete growth hormone (GH), prolactin (PRL), adrenocorticotropin (ACTH), thyroid-stimulating hormone (TSH), and the gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) [5].

Somatotrophs, or GH cells, constitute approximately 50% of adenohypophysial cells. They are located mainly in the lateral wings of the pars distalis; scattered somatotrophs can also be demonstrated in the median wedge. Somatotrophs are spherical or oval medium-sized cells containing numerous secretory granules that give a strong positivity for GH by immunohistochemistry.

Lactotrophs, or PRL cells, represent 10% to 25% of adenohypophysial cells. They are randomly located throughout the pars distalis. They are oval or irregular, small or medium-sized, and sparsely granulated cells, most frequently showing a globular or ring-like immunopositivity for PRL over the Golgi complex.

Corticotrophs produce ACTH and several related peptides, such as β-lipotropin (β-LPH) and endorphins. They constitute 10% to 20% of adenohypophysial cells and are mainly located in the central mucoid wedge or median wedge portion. Corticotrophs are oval or angular, medium-sized or large, and usually densely granulated cells exhibiting strong cytoplasmic immunopositivity for ACTH.

Thyrotrophs, or TSH cells, constitute less than 10% of adenohypophysial cells. Located mainly in the anteromedial portion of the pars distalis, they are polyhedral or angular and large or medium-sized cells possessing long cytoplasmic processes.

* Corresponding author.
E-mail address: sanno-n@nms.ac.jp (N. Sanno).

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They show a fine granular positivity for TSH by immunohistochemistry.

Gonadotrophs, or FSH/LH cells, representing approximately 10% of adenohypophysial cells, are randomly located. They are medium-sized or small cells and are spherical or oval. Both FSH and LH are present in the cytoplasm of the same cell.

Classification of pituitary tumors

By histologic staining affinity, the earliest classification divided pituitary adenomas into acidophilic, basophilic, and chromophobic types. Based on clinical considerations, acidophilic adenomas were assumed to produce GH, basophilic adenomas were thought to produce corticotropin, and chromophobic adenomas were considered to be endocrinologically inactive.

Current morphologic classifications are based on hormonal content and ultrastructural morphology [1,2,5–7]. As outlined in Table 1, this functional classification recognizes 14 primary pituitary adenoma subtypes, each having its own morphologic, immunohistochemical, and biologic profile. More recently, Kovacs et al [8] proposed a revised classification of adenohypophysial neoplasms to the World Health Organization (WHO). It represents a five-tier classification. The first level distinguishes pituitary tumors based on the clinical symptoms and blood hormone levels of the patients. The second level is based on neuroimaging and intraoperative data and includes tumor size, extension, and invasiveness. The third level is based on histologic examination with routine staining, such as hematoxylin–eosin (HE) and periodic acid–Schiff (PAS) as well as silver staining for reticulin fibers to exclude the presence of nontumorous or hyperplastic tissue. The fourth level is based on the demonstration of hormone content by immunocytochemistry. The fifth level is represented by ultrastructural features of the tumor cell. The ultrastructural examination provides precise cellular derivation. Herein, we describe different types of pituitary adenomas based on the ultrastructural approach in correlation with the other levels of classification.

Table 1
Classification and frequency of pituitary adenomas in unselected surgical material

Adenoma type	Frequency (%)
Densely granulated GH	6.85
Sparsely granulated GH	6.44
Densely granulated PRL	0.48
Sparsely granulated PRL	26.85
Mixed GH and PRL cell	4.04
Mammosomatotroph	1.44
Acidophilic stem cell	1.98
Corticotroph	10.14
Silent corticotroph subtype 1	1.50
Silent corticotroph subtype 2	2.26
Silent subtype 3	1.37
Thyrotroph	0.96
Gonadotroph	9.04
Null cell	14.11
Oncocytoma	11.14
Unclassified, plurihormonal	1.10

Abbreviations: GH, growth hormone; PRL, prolactin.

Growth hormone–secreting adenomas

GH-secreting pituitary lesions are associated with acromegaly or gigantism. A variety of histologic findings can be revealed, including (1) densely granulated somatotroph adenoma; (2) sparsely granulated somatotroph adenoma; (3) mixed somatotroph-lactotroph adenoma; (4) acidophil stem cell adenoma; (5) mammosomatotroph adenoma; (6) plurihormonal adenoma producing GH and one or more glycoprotein hormones, principally α-subunit; (7) somatotroph carcinoma; (8) somatotroph hyperplasia; and (9) no distinct morphologic change. Densely granulated somatotroph adenomas and sparsely granulated somatotroph adenomas are the most commonly occurring tumors in patients with acromegaly; bihormonal somatotroph-lactotroph adenomas and mammosomatotroph adenomas occur most often in young individuals with gigantism. Rarely, somatotroph adenomas are not associated with signs of GH overproduction and are consequently called silent. The reported silent cases are sparsely granulated or atypical somatotroph adenomas [9].

Densely granulated somatotroph adenomas

On HE staining, the adenoma is composed of acidophilic PAS-negative cells with a diffuse, trabecular, or sinusoidal pattern (Fig. 1). By immunohistochemistry, strong cytoplasmic immunoreactivity for GH is evident in most adenoma cells. Other immunoreactivity may also be present for PRL, α-subunit, TSH, or, rarely, FSH or LH [10,11]. In situ hybridization study shows signal for GH mRNA diffusely in cytoplasm. Occasionally, PRL, α-subunit, TSH, FSH, and LH signals are also present [12,13]. Ultrastructural analysis reveals that densely granulated somatotroph

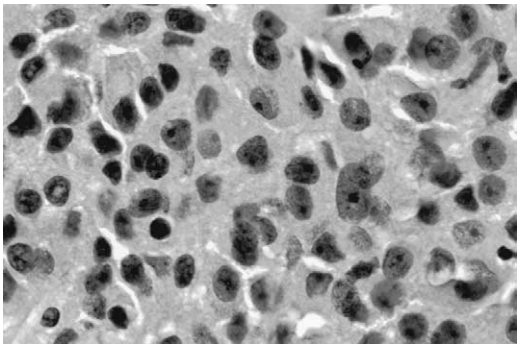

Fig. 1. Hematoxylin–eosin-stained section of a densely granulated growth hormone adenoma showing cells with pleomorphic nuclei and abundant cytoplasm (original magnification × 350).

adenomas consist of uniform, polyhedral, or elongate cells with a predominantly spherical or ovoid nucleus. The rough endoplasmic reticulum (RER) is usually well developed, and the Golgi apparatus is prominent. The mature secretory granules are numerous and measure 150 to 600 nm (mainly 400–500 nm) in diameter (Fig. 2).

Sparsely granulated somatotroph adenomas

These tumors are chromophobic on HE sections and consist of cells that often show considerable variation in shape and size. In some cells, the nucleus has a crescent shape and is pushed at the periphery by a globular structure corresponding to the fibrous body at the ultrastructural level. A prominent Golgi area sometimes resembles a fibrous body. GH immunoreactivity is generally moderate to weak. By in situ hybridization, the signal for GH mRNA is weaker than that of the densely granulated type [14,15]. The secretory granules may be extremely scanty and usually measure 100 to 200 nm. The most recognizable structure of this tumor type is the "fibrous body," which is immunoreactive for keratin and located in the Golgi region adjacent to the nucleus (Fig. 3) [16].

The mixed somatotroph-lactotroph adenomas, acidophilic stem cell adenomas, and mammosomatotroph adenomas are bihormonal tumors producing both GH and PRL.

The mixed somatotroph-lactotroph adenoma is most commonly composed of densely granulated somatotrophs and sparsely granulated lactotrophs [1]. On HE-stained sections, these tumors consist of acidophilic cells interspersed with chromophobic cells. By immunohistochemistry, GH and PRL are demonstrated in different cell populations. Electron microscopy documents the bimorphous nature of the tumor (Fig. 4).

Acidophilic stem cell adenomas are chromophobic or slightly acidophilic tumors exhibiting no PAS positivity. They are monomorphous and consist of one cell type that produces both GH and PRL (Fig. 5). Acidophilic stem cell adenomas are assumed to originate in the common precursor cell of somatotrophs and lactotrophs; they usually occur in younger individuals and grow faster than other tumors [17].

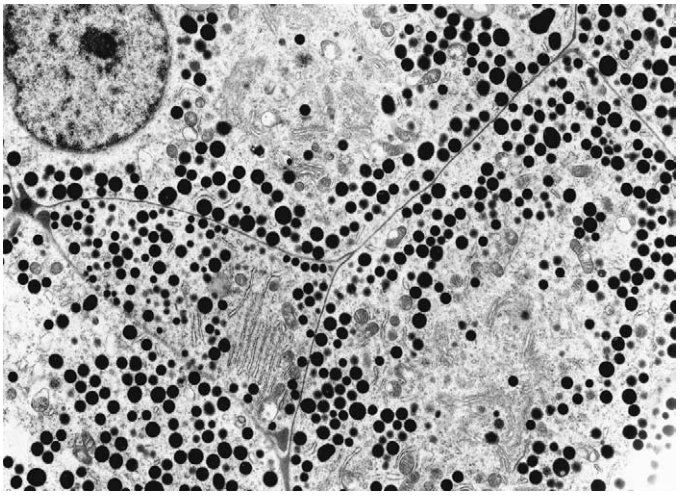

Fig. 2. Densely granulated growth hormone cell adenoma with numerous large secretory granules 200 to 600 nm in diameter (original magnification × 9680).

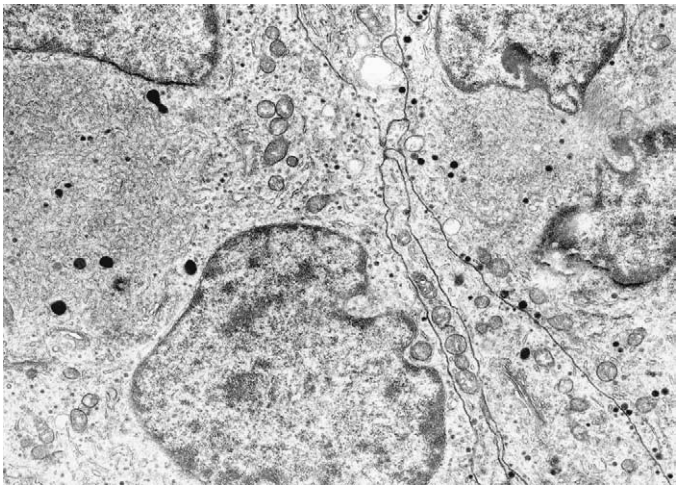

Fig. 3. Sparsely granulated growth hormone cell adenoma Note the small (less than 200 nm) scant secretory granules and the fibrous body (*asterisk*) trapping secretory granules, mitochondria, and a few lysosomes (original magnification × 12,320).

Mammosomatotroph adenoma is morphologically similar to densely granulated somatotroph adenoma. The adenoma cells are strongly acidophilic and monomorphous. Immunocytochemistry shows that the same cells are immunoreactive for both GH and PRL. Immunoreactivity for PRL is variable, and a number of these tumors also contain α-subunit of glycoprotein hormones. The diagnosis is confirmed by electron microscopy [18,19]. The ultrastructural immunogold technique localizes both GH and PRL within the same cell and even within the same secretory granule.

Plurihormonal adenomas produce GH and one or more glycoprotein hormones, primarily α-subunit. Patients have acromegaly and elevated serum GH levels. Immunohistochemistry demonstrates the presence of cells producing GH and α-subunit. By electron microscopy, the appearance of tumors is chiefly monomorphous, similar to that of densely granulated GH cell adenomas. Using *in situ*

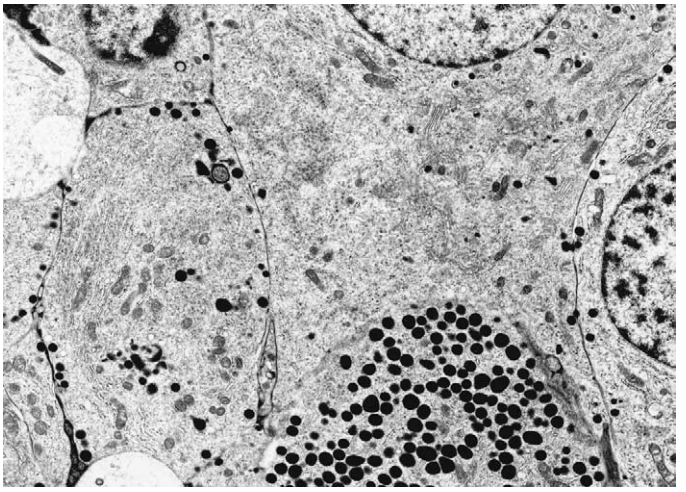

Fig. 4. Mixed adenoma consisting of sparsely granulated prolactin (PRL) cells and densely granulated growth hormone cells. Note the rough endoplasmic reticulum and the large Golgi apparatus. They are typical features of PRL cells. Note exocytoses (*arrows*) (original magnification × 8400).

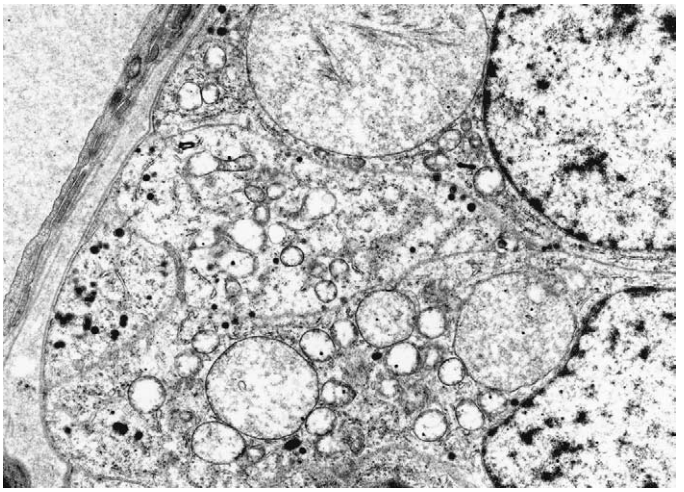

Fig. 5. Acidophilic stem cell adenoma displaying the characteristic oncocytic change with development of giant mitochondria. There are misplaced exocytoses (*arrow*).

hybridization, multiple gene expression is also recognized [12–14]. The reasons for plurihormonality are not understood. One explanation implicates multidirectional differentiation of pluripotential stem cells. This theory suggests that the tumors arise from undifferentiated cells and should be associated with greater growth rate and more aggressive clinical behavior.

Prolactin-secreting pituitary adenomas

The lactotroph adenomas are the most common pituitary tumor types are associated with hyperprolactinemia. Clinically, amenorrhea, galactorrhea, infertility, decreased libido, and impotence may be evident. Men and postmenopausal women usually come to medical attention because of symptoms of a pituitary mass, such as headache and visual field deficits or ophthalmoplegia. The most common visual abnormality is bitemporal hemianopsia secondary to compression of the optic chiasm.

The lactotroph adenomas are chromophobic or slightly acidophilic, with a diffuse histologic pattern. Small tumors may rarely be papillary. The presence of calcification and endocrine amyloid deposits has been noted in several cases. PRL cell adenomas are predominantly monohormonal, containing only immunoreactive PRL. Strong immunoreactivity for PRL in the Golgi region at one side of the nucleus of adenoma cells is a characteristic finding. Diffuse cytoplasmic immunostaining is noted in the rare densely granulated variant. By in situ hybridization, diffuse cytoplasmic labeling for PRL is shown (Fig. 6).

By electron microscopy, cells of sparsely granulated PRL cell adenoma have the striking appearance of hormonally active PRL cells. The cytoplasm contains abundant RER and a prominent Golgi apparatus with pleomorphic immature secretory granules (Fig. 7). The cytoplasmic storage granules are sparse, measuring 120 to 300 nm in size, and granule extrusions may occur at the basal portion of cell facing the perivascular space (orthotopic exocytosis) or at the lateral cell surfaces far from the basement membrane (misplaced exocytosis) [20,21].

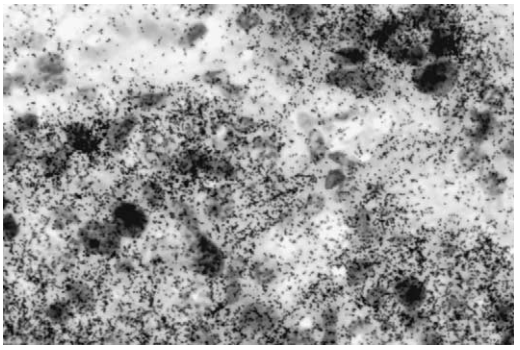

Fig. 6. Prolactin adenoma analyzed by *in situ* hybridization with a ^{35}S-labeled oligonucleotide probe showing diffuse labeling of the tumor cells in the paraffin section (original magnification × 350).

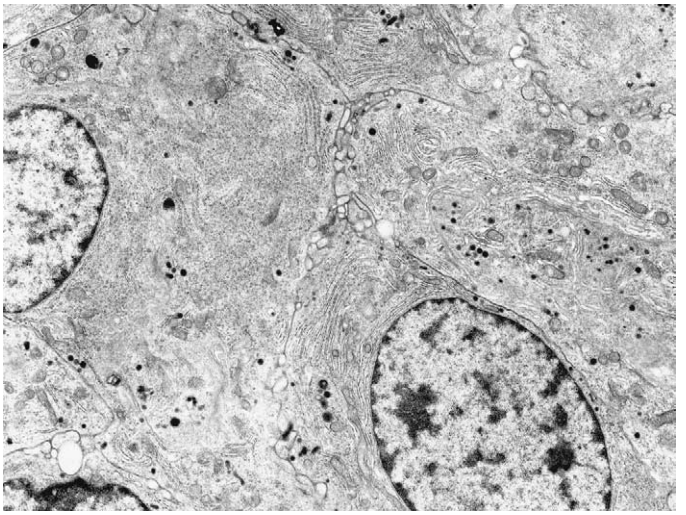

Fig. 7. Sparsely granulated prolactin cell adenoma endowed with typical features: abundant rough endoplasmic reticulum and prominent Golgi apparatus and misplaced exocytosis (original magnification × 8400).

The rare densely granulated variant consists of middle-sized elongate or polyhedral cells, in which the RER and Golgi membranes are less prominent than in the sparsely granulated form. The secretory granules are much larger (up to 600–700 nm) and more numerous.

The medical treatment of hyperprolactinemia using bromocriptine and other dopaminergic agonists influences the pathologic appearance of PRL-secreting adenomas. As opposed to the uniform morphology of untreated tumors, PRL cell adenomas exposed to dopamine agonists display a great variety of appearances [22–27]. The PRL-secreting adenoma that has been suppressed by dopamine agonists contains scant (sometimes, barely detectable) PRL immunoreactivity. By electron microscopy, the tumor consists of small cells with markedly heterochromatic and multiple indented nuclei as well as a narrow rim of cytoplasm containing a few membranous organelles and secretory granules (Fig. 8). In addition, some tumors contain a mixed population of suppressed cells

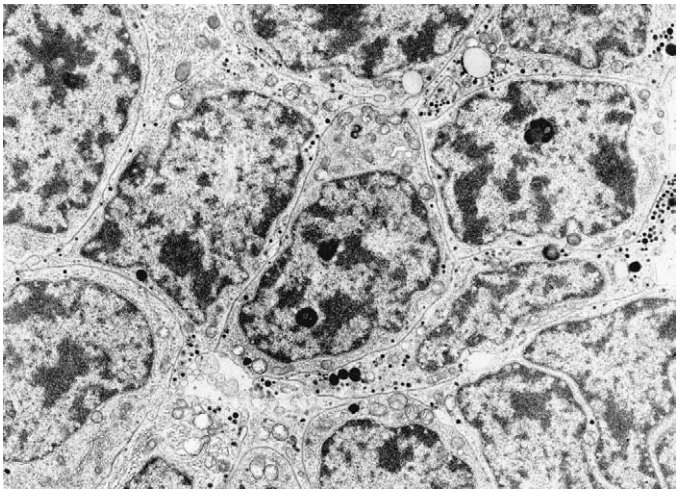

Fig. 8. Sparsely granulated prolactin cell adenoma treated with bromocriptine. Compared with untreated tumors (see Fig. 7), the nuclei are heterochromatic, the size of cells is small, and the cytoplasm contains scanty organelles (original magnification × 8400).

and cells displaying varying degrees of synthetic activity. Protracted medical treatment of PRL-secreting adenomas may lead to marked perivascular and interstitial fibrosis [28]. If extensive, chances for successful surgery may decrease. Approximately 5% to 10% of tumors do not respond to a dopaminergic agent. In such resistant cases, neither a significant decrease in the serum PRL concentration nor morphologic signs of suppression are noted. Some reports show a decreased number of dopamine D_2 receptor in such tumors [29]. PRL cell carcinoma is rare, and only a few cases have been reported [30].

Adrenocorticotropin-secreting pituitary adenomas

Cushing's disease is caused by a corticotroph cell adenoma of the anterior pituitary. The clinical features of Cushing's disease are the results of chronic exposure to hypercortisolemia. Signs include weight gain, centripetal obesity, moon face, abdominal purple striae, easy bruisability, proximal myopathy, hypertrichosis, and psychiatric disturbances. Excessive glucocorticoid levels may cause osteoporosis, insulin resistance, and glucose intolerance in many patients.

Only about half of the adenomas causing Cushing's disease are detectable by CT or MRI, because these tumors may be quite small [3,31], measuring less than 1.0 cm in diameter. Macroadenomas are a rare cause of Cushing's disease and are usually invasive and difficult to cure. It should be remembered that patients with ectopic corticotropin syndrome may have incidental nonfunctioning adenomas; this emphasizes the importance of making the correct diagnosis based on biochemical tests.

The tumor cells are basophilic and stain positively with the PAS method. Immunohistochemistry demonstrates the presence of corticotropin and other Pro-Opiomelanocortin (POMC)-related peptides, such as endorphins and β-lipotropin, in the cytoplasm of adenoma cells [32,33]. Corticotropin-secreting adenomas are most often monomorphous and monohormonal. Rarely, they may be immunopositive for α-subunit, LH, or PRL [6,34].

The electron microscopic findings of corticotroph adenomas are characteristic and diagnostic. The adenoma cells are elongate or angular, with ovoid nuclei that may show some indentation. The cytoplasm is abundant and possesses prominent RER membranes, free ribosomes and polysomes, a prominent Golgi complex, and many secretory granules in the size range of 150 to 450 nm (most commonly, 300–350 nm) (Fig. 9). The most important diagnostic markers are bundles of reticulin immunoreactive intermediate filaments located chiefly in the perinuclear region (see Fig. 8). Excessive accumulation of these filaments (Crooke's hyalinization) occurs in surrounding nontumorous corticotroph cells as well as in some adenoma cells [5,32,33,35]. In these adenoma cells, the filaments occupy a large part of the cytoplasm, displacing organelles and secretory granules to the cell periphery (Fig. 11).

Nelson's syndrome is caused by an aggressive ACTH-secreting pituitary adenoma in patients

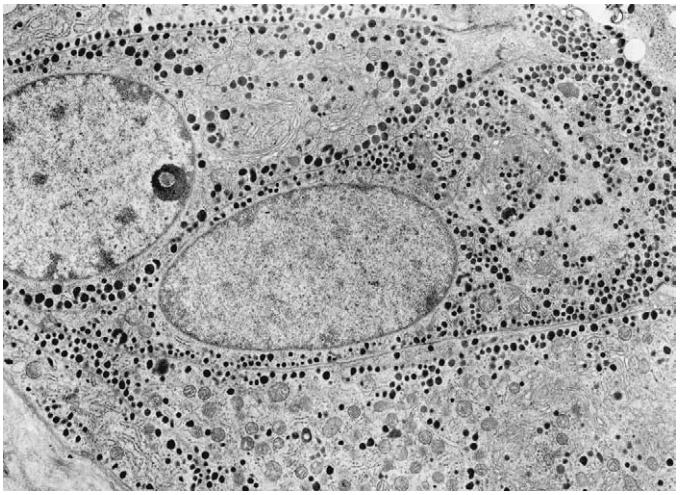

Fig. 9. Corticotroph cell adenoma with numerous secretory granules. The cytokeratin filaments are scanty. Some cytokeratin filaments are seen around the Golgi apparatus (original magnification × 8400).

who have undergone bilateral adrenalectomy for Cushing's disease [31]. In contrast to the tumors of Cushing's disease, these tumors are usually macroadenomas, with symptoms caused by the large tumor size, including headaches and visual field defects. The high corticotropin levels cause hyperpigmentation. The tumor is basophilic, PAS-positive, and immunopositive for corticotropin and other POMC-related peptides. The electron microscopic features of the tumor cells are indistinguishable from those of Cushing's disease, except for the absence of intermediate filaments in the cell cytoplasm.

Another tumor type is the silent corticotroph adenoma subtype 1. These tumors are unassociated with clinical or biochemical evidence of corticotropin hypersecretion, and patients are diagnosed at the macroadenoma stage as having a nonsecreting pituitary adenoma. Morphologically, these tumors are indistinguishable from those of Cushing's disease, and the tumor cells are immunoreactive for corticotropin and other POMC-related peptides. On electron microscopy, there are no differences between silent corticotroph adenoma and the clinically active corticotropin adenoma. In situ hybridization studies have revealed that silent corticotroph adenomas contain the POMC gene [36]. Disturbance of POMC processing is thought to be the reason for the absence of clinical symptoms in patients with these tumors [36].

Silent corticotroph adenoma subtype 2 is morphologically and immunohistochemically similar to subtype 1. Variable PAS positivity and immunoreactivity for POMC-derived peptides are found. Ultrastructurally, the adenomas are well differentiated and consist of polyhedral cells without polarity. The secretory granules are smaller (200–300 nm) than those of functional corticotrophs. No intermediate filaments are found in the cytoplasm (Fig. 10).

Silent subtype 3 was originally thought to consist of POMC-producing cells, because variable immunoreactivity for corticotropin and other POMC-related peptides was observed. Scattered adenoma cells may be immunoreactive for GH, PRL, or one or more glycoprotein hormones. Ultrastructurally, these tumors are composed of large and polar cells. The cytoplasm contains a well-developed Golgi apparatus (Fig. 12). The secretory granules measure approximately 200 nm; they are numerous and are disposed at one pole of the cytoplasm, resembling well-differentiated glycoprotein hormone–producing cells [37,38].

Thyrotropin-secreting adenomas

The TSH-secreting adenoma is the rarest type of pituitary tumor, representing less than 1% of total pituitary adenomas. Clinically, TSH-secreting adenomas present with the symptoms of hyperthyroidism. A syndrome of inappropriately normal or elevated secretion of TSH despite elevated serum thyroid hormone levels is the most important

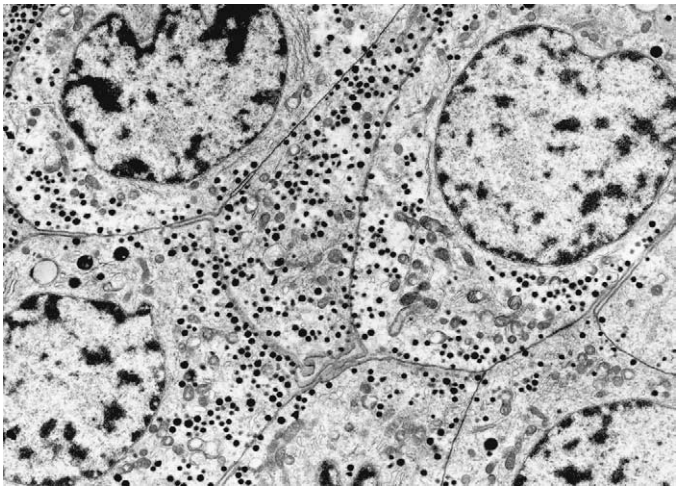

Fig. 10. Silent corticotroph adenoma subtype 2. The morphology of the secretory granules in subtype 2 tumors shows a similarity to that of corticotrophs, but the former are smaller. The average size of the adenoma cells is also smaller. Cytokeratin filaments are not present in subtype 2 tumors (original magnification × 8400).

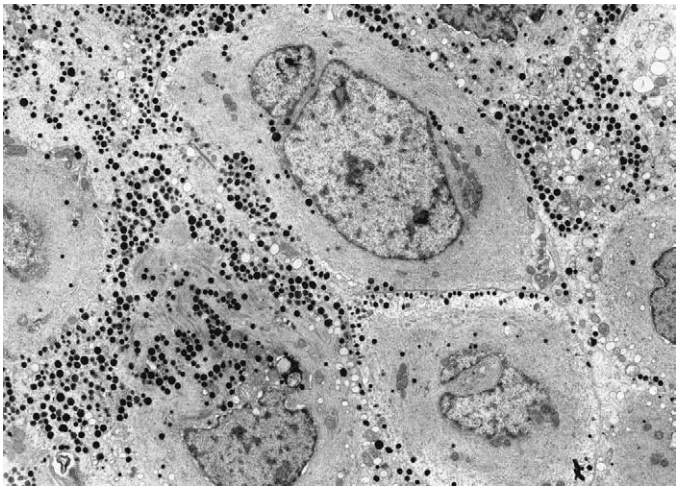

Fig. 11. Corticotroph cell adenoma displaying advanced Crooke's hyalinization. Most of the cytoplasm is occupied with a thick ring of cytokeratin filaments displacing secretory granules to the cell periphery (original magnification × 6300).

diagnostic criterion distinguishing a TSH-secreting adenoma from primary hyperthyroidism.

The tumor secretes an excess of free α-subunit, resulting in molar ratio of α-subunit to TSH of greater than 1.0.

TSH-secreting adenomas are composed of chromophobic angular-shaped cells with a sinusoidal or diffuse pattern. Massive fibrosis may be apparent in some thyrotroph adenomas. By immunohistochemistry, the adenoma cells are positive for α-subunit of TSH and β-subunit of glycoprotein hormones. TSH-secreting adenomas often cosecrete GH and PRL [39]. By in situ hybridization study, gene expression of β-TSH and α-subunit as well as GH and PRL is observed [40].

By electron microscopy, the tumor cells are elongated and possess long cytoplasmic processes and a spherical or ovoid nucleus with prominent nucleoli. The RER and Golgi complexes are moderately developed, and cytoplasmic microtubules often form a rich network. The small secretory granules measure between 50 and 200 nm in diameter and are arranged peripherally under the plasmalemma (Fig. 13).

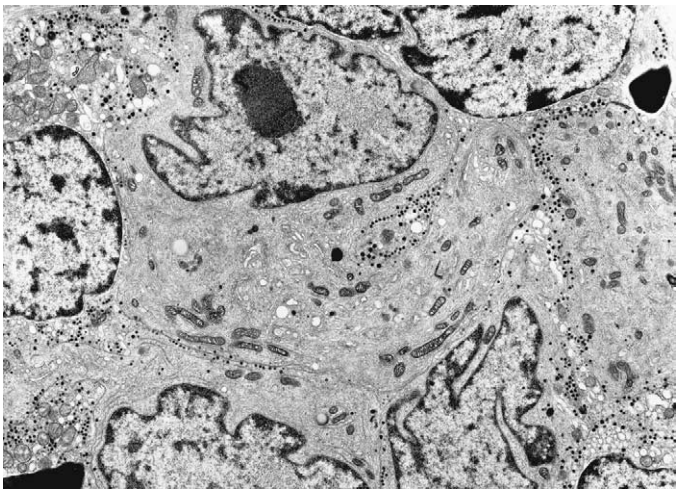

Fig. 12. Silent corticotroph cell adenoma subtype 3. The cells of these tumors are large, and nuclear pleomorphism is often marked. The large cytoplasm is packed with rough endoplasmic reticulum, often smooth endoplasmic reticulum, and a prominent Golgi apparatus. The secretory granules are always small (original magnification × 7500).

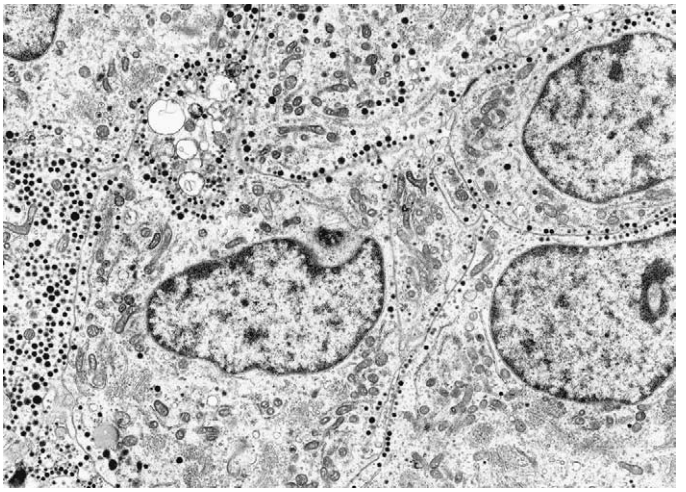

Fig. 13. Thyrotroph cell adenoma. The angular shape of cells is accentuated by the peripheral localization of small secretory granules (original magnification × 8400).

Gonadotropin-secreting adenomas

Gonadotroph adenomas are identified by increased serum levels of FSH, LH, or α-subunit. Clinical symptoms are a sellar mass with visual failure and hypopituitarism. Instead of the rare hypergonadism, these tumors typically present with hypogonadism. Gonadotroph adenomas are detected most frequently in middle-aged men. In postmenopausal women, the clinical diagnosis is rather difficult, because the circulating FSH/LH levels are physiologically elevated [41–43].

Histologically, gonadotroph adenomas are chromophobic adenomas with a sinusoidal pattern, often showing pseudorosettes or a papillary pattern. Immunohistochemically, β-subunit of FSH, α-subunit of glycoprotein, and β-subunit of LH are positive in the cytoplasm of tumor cells. By *in situ* hybridization study, staining for gonadotropin subunit mRNA is shown in the cytoplasm of tumor cells (Fig. 14). Electron microscopically, gonadotroph adenomas of the male type show considerable variability regarding the degree of functional differentiation. Generally, these adenomas have a slightly dilated RER and a prominent Golgi complex with sparse secretory granules measuring 200 nm in diameter (Fig. 15). Varying degrees of oncocytic change are observed in approximately 50% of gonadotroph adenomas in men [20,44]. Gonadotroph adenomas of female type appear different from those of the male type [44]. The sparsely granulated tumor cells are characterized by a unique morphologic marker, the "honeycomb Golgi complex" (Fig. 16). The sacculi of the Golgi apparatus transform into clusters of spheres containing a low-density proteinaceous substance. The mechanism and functional significance of these changes are not known.

Nonsecretory adenomas: null cell adenoma and oncocytoma

Nonsecreting or nonfunctioning adenomas are characterized by the absence of clinical syndromes and the absence of elevated hormone concentrations. They represent approximately 25% of

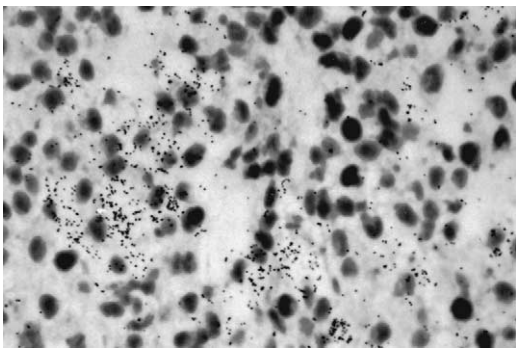

Fig. 14. *In situ* hybridization for luteinizing hormone (LH) in a gonadotroph adenoma using frozen tissue with a ^{35}S-labeled oligonucleotide probe. Staining for LH mRNA is shown by the black-silver grains (original magnification × 300).

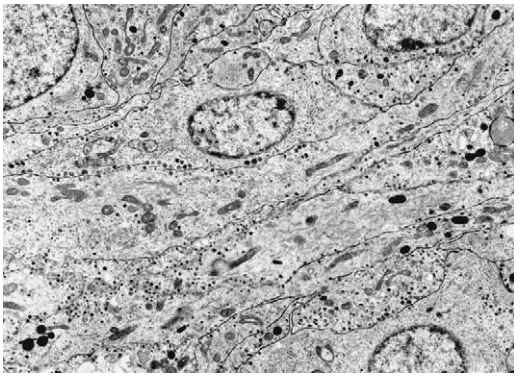

Fig. 15. Gonadotroph adenoma, male type, featuring uniform euchromatic nuclei, slightly dilated rough endoplasmic reticulum, a prominent Golgi complex with regular appearance, and small secretory granule accumulation in cell processes (original magnification × 8400).

surgically removed adenomas and are large macroadenomas occurring predominantly in older age groups [3].

Histologically, these adenomas are chromophobic or slightly acidophilic with a diffuse pattern. Immunohistochemically, the tumor cells are often positive for one or more hormones, including α-subunit of glycoprotein hormones and β-subunit of FSH, LH, TSH, and, occasionally, GH, PRL, or ACTH. Some of the null cell adenomas have immunoreactivity for neuron-specific enolase, chromogranin, or synaptophysin [25]. *In situ* hybridization studies often show gene expression for those hormones in a variety of cases [45,46]. The recent development of hormone assay and morphologic studies may increase the recognition of glycoprotein (gonadotropin)–secreting adenomas [47]. The ultrastructure of null cell adenoma contains small cytoplasm harboring poorly developed RER and Golgi membranes and scanty small (less than 250 nm) secretory granules (Fig. 17) [48].

Oncocytomas are characteristic on electron microscopy because of abundant mitochondrial accumulation in the cell cytoplasm. Despite the marked mitochondrial abundance, RER, Golgi complex, and secretory granules are always recognized (Fig. 18) [49]. All other features of this tumor type are similar to those of null cell adenomas. A considerable proportion of null cell adenomas/oncocytomas display minor immunoreactivity for glycoprotein hormones, and by in situ hybridization, they also express genes for α-subunit and β-subunit of glycoprotein hormones [45,56]. Gene expression for other hormones, such as GH, PRL, or corticotropin, is also detected [46]. From these observations, it can be seen that gonadotroph cell adenomas and the null cell adenoma/oncocytoma group obviously overlap; thus, it is difficult to draw the line between the two entities.

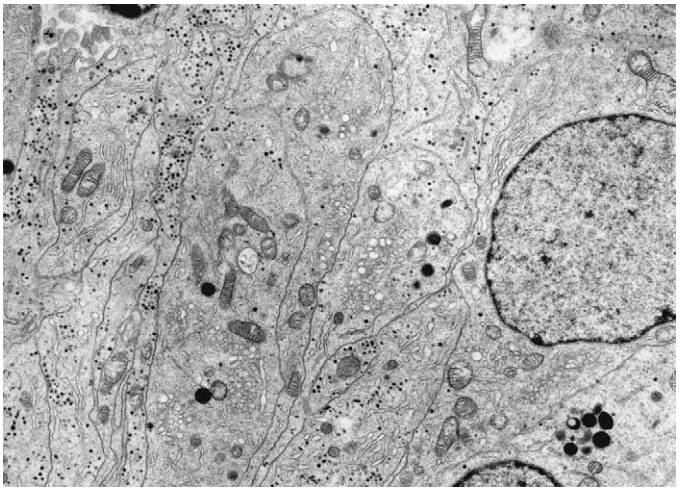

Fig. 16. Gonadotroph adenoma, female type. The polarity of cells and uneven distribution of small (100–150 nm) secretory granules are similar to those seen in tumors in men. The diagnostic marker of the tumor type is the honeycomb Golgi complex, the vacuolar transformation of the Golgi complex (original magnification × 8400).

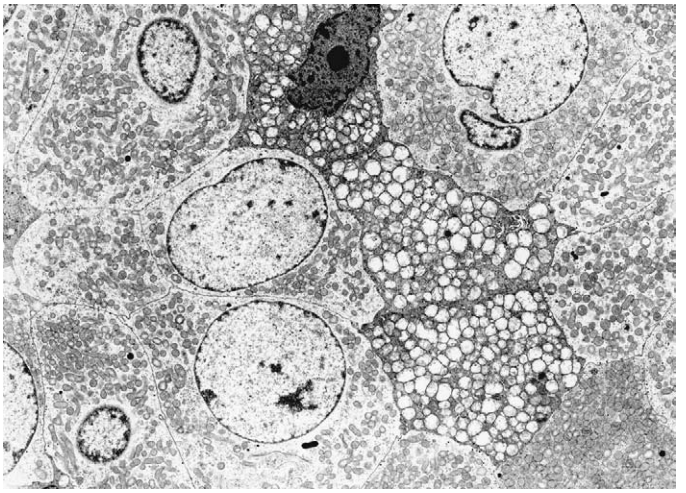

Fig. 17. Null cell adenoma with poorly developed rough endoplasmic reticulum and Golgi complex and scant secretory granules (original magnification × 8400).

Plurihormonal adenomas

Plurihormonal adenomas are tumors that are capable of producing more than one hormone. Plurihormonality is observed in mixed GH-PRL cell adenomas or in mammosomatotroph and acidophilic stem cell adenomas. In other cases, various combinations may occur, such as GH and TSH; GH, PRL, and TSH; GH, PRL, and ACTH; and GH, PRL, TSH and α-subunit. The cytogenesis of these tumors is not understood. A discrepancy between hormone expression and gene expression has been reported.

Pituitary carcinomas

Pituitary carcinomas are rare and can be diagnosed only when craniospinal or systemic metastases are present [30,50]. According to a recent review, 64 pituitary carcinomas have been reported in the literature [30]. Seventy-four percent of reported cases are hormone secreting, whereas 26% are endocrinologically nonsecreting. Among functioning carcinomas, the most common type is PRL cell carcinoma, followed by corticotropin-secreting carcinomas. Only five GH-secreting tumors and one TSH-secreting tumor have been

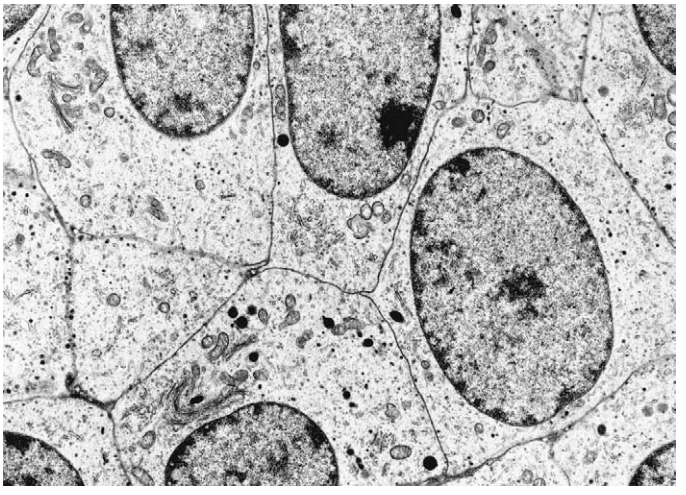

Fig. 18. Pituitary oncocytoma showing abundance of mitochondria (original magnification × 4480).

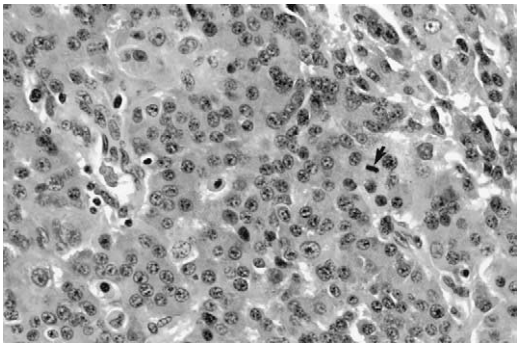

Fig. 19. Corticotropin carcinoma metastatic to the liver in a patient with Nelson's syndrome. The tumor cells have large nuclei and prominent mitoses (*arrow*) (original magnification × 250).

reported to date to our knowledge. ACTH-secreting carcinomas are often associated with symptomatic spread (liver, lung, bone, and lymph nodes).

Histologically, the patterns of tumor growth and cellular pleomorphism are variable. Mitotic figures, nuclear atypia, and hyperchromatic nuclei are variable. Cytologic atypia is more prominent in the metastases than in the primary tumors (Fig. 19). Immunohistochemistry shows immunoreactivity for the secreted hormone in carcinoma cells. The Ki-67 proliferation index of carcinoma varies from case to case, ranging from 0% to 22% [51], and is significantly increased compared with that in pituitary adenomas in most cases. *Ras* mutations are detected in PRL carcinomas [52]. Increased p53 proto-oncogene expression in pituitary carcinomas is also reported [53]. Gene alterations in oncogene or tumor suppressor genes may be related to tumorigenesis [54,55,57].

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