PITUITARY HISTOPATHOLOGY IN MAN: NORMAL AND ABNORMAL

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THE NORMAL PITUITARY GLAND

The pituitary is a bean-shaped gland located at the base of the brain in the midline. It measures 0.6 cm SI x 0.9 cm AP x 1.3 cm and an average gland weighs 0.6 grams. Females tend to have larger glands, especially during or after pregnancy, with weights up to 1 g (1;2). The gland lies within the bony sella turcica that surrounds it inferiorly and laterally. Superiorly it is covered by the diaphragma sella, a reflection of the dura mater (3;4). Lateral to the sella are the cavernous sinuses; anteroinferior is the sphenoid sinus; anterosuperior is the optic chiasm; superior to it is the hypothalamus. The pituitary is composed of two anatomically and functionally distinct parts: the neurohypophysis and the adenohypophysis. (Figure 1)

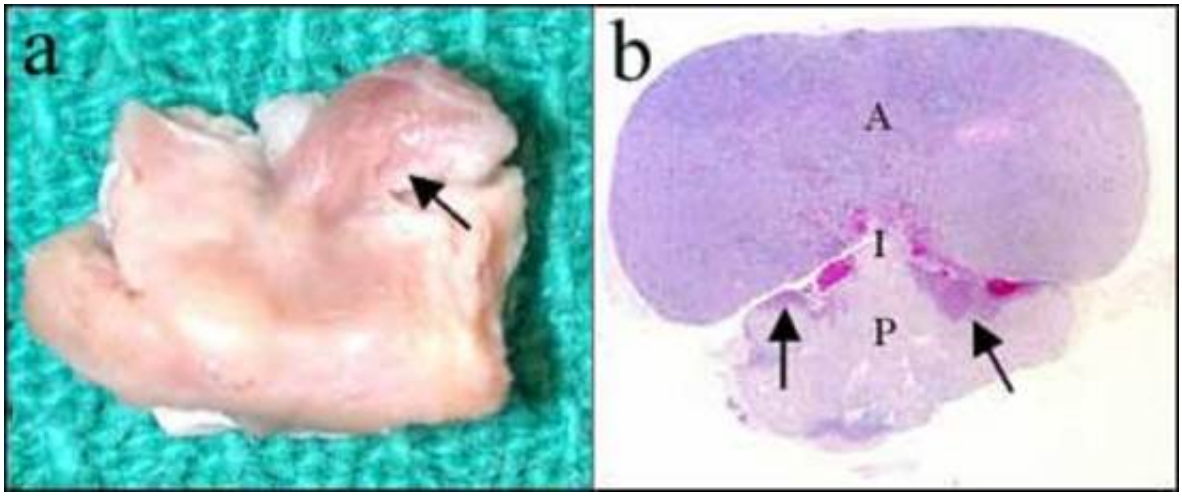

Figure 1. (a) The normal pituitary gland is a bean-shaped structure that hangs from the pituitary stalk (arrow), an extension of the hypothalamus that traverses the diaphragm of the sella turcica. (b) A horizontal section of the gland identifies the anterior lobe (A) or

“adenohypophysis”, the posterior lobe (P) or “neurohypophysis” and the vestigial intermediate lobe (I) that is poorly developed in humans. This gland demonstrates “basophil invasion” of the posterior lobe, proliferation of corticotrophs into the neurohypophysis (arrows) that is a normal feature in older patients.

The neurohypophysis is composed of the infundibulum, the pituitary stalk, and the pars nervosa of the pituitary. The cell types of the neurohypophysis include pituicytes, which are modified glial cells, and the axonal processes of neurons whose cell bodies are located in the hypothalamus. The neurohypophysis stores and releases the hypothalamic hormones oxytocin and vasopressin (Figure 2).

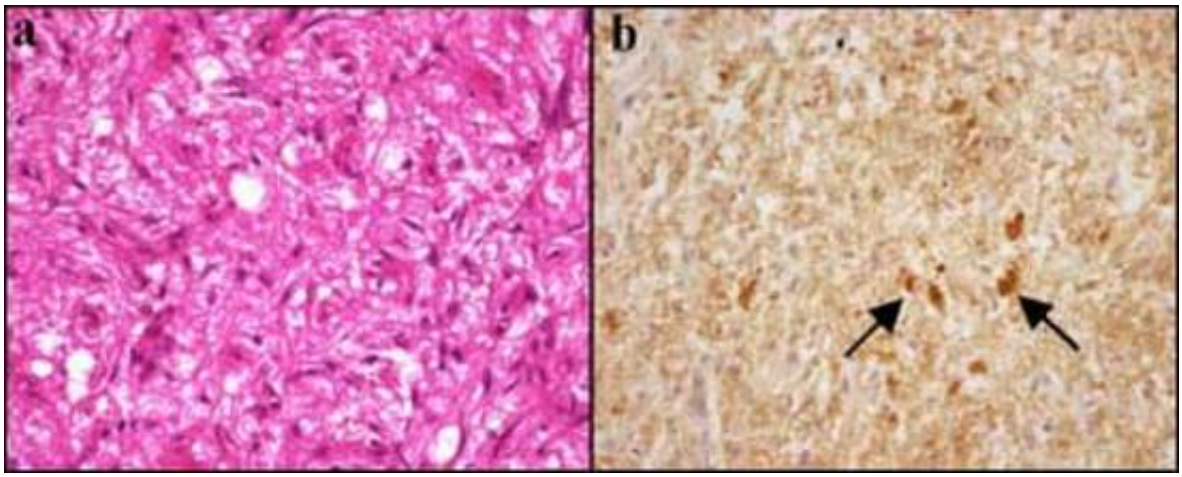

Figure 2. (a) The neurohypophysis is composed of “pituicytes”, modified glial cells, that surround axonal processes of neurons whose cell bodies are located in the hypothalamus. Occasional dilated terminals of those axons are seen as “Herring bodies” (arrows). (b) The neurohypophysis stores and releases the hypothalamic hormones oxytocin and vasopressin in Herring bodies that are best identified with immunostains for the hormones, as seen here stained for vasopressin (arrows).

The adenohypophysis is of endodermal origin, embryologically derived from Rathke’s pouch (5). It has three regions, the pars distalis or anterior lobe, the pars intermedia or intermediate lobe and the pars tuberalis, an extension of epithelium that wraps around the infundibulum of the pituitary stalk. Adenohypophyseal development and cytodifferentiation are regulated by highly specific transcription factors (6-8). (Figure 3) Many of these are implicated in early pituitary organogenesis, including the Rathke’s pouch homeobox (Rpx) protein which is identified in the pituitary primordium prior to the onset of known pituitary hormone production, and Pax-6. Mutations of the former have been associated with septo-optic dysplasia and deficiency of the latter is associated with the small-eye mouse phenotype. The bicoid-related pituitary homeobox

factor Ptx1 and structurally related pituitary homeobox factor 2 (Ptx2) are also required for pituitary development. Two members of the Lhx gene family, a group of LIM homeobox genes, Lhx3 and Lhx4 and P-LIM, another LIM homeobox protein transcription factor, are expressed in the pituitary with highest levels at the early stages of Rathke's pouch development. Loss of both Lhx-3 and Lhx-4 results in pituitary hypoplasia but deficiency of Lhx-4 only results in loss of pituitary gonadotrophs alone. Another early determinant of pituitary differentiation is the Prophet of Pit-1 (PROP-1) is a paired-like homeodomain protein that is expressed early in pituitary development. It induces expression of the next phase of development directed by the pituitary transcription factor Pit-1, and plays a role in downregulation of Rpx. Inactivating mutations of PROP-1 have been identified as the cause of Pit-1 deficiency in Ames dwarf mice and of combined pituitary hormone deficiency in humans. Id, a member of the helix-loop-helix (HLH) family of transcription factors, Isl-1, a Lim factor, and several other transcription factors are also found early in development and have been implicated in developmental anomalies.

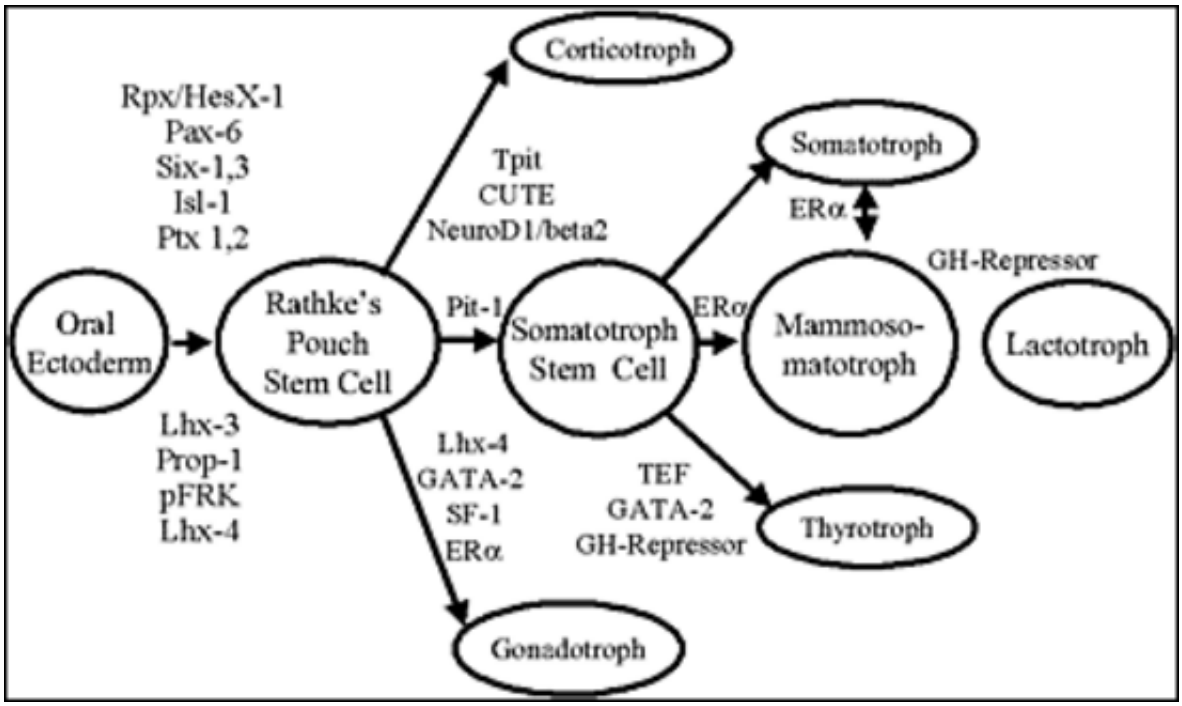

Figure 3. Pathways of pituitary development and cytodifferentiation. Transcription factors implicated in each step are identified. (see text for details)

The adenohypophysis is composed of acini that contain the specialized cell types, all of which have their own unique hormonal function and characteristics. The molecular factors that determine hormone production are transcription factors that target specific hormone genes. These factors have clarified three main pathways of cell differentiation (6;7) (Figure 3).

Somatotrophs, lactotrophs, mammosomatotrophs, and thyrotrophs all derive from growth hormone (GH)-producing precursors that express the transcription factor Pit-1 (9). (10-12)The

expression of estrogen receptor (ER)α enhances prolactin (PRL) secretion (13), allowing mammosomatotroph differentiation, and a silencing mechanism is thought to repress GH production to allow mature lactotrophs to develop. Thyrotroph embryonic factor (TEF) is the putative factor required for thyrotrophin (TSH)-beta production (14), and GATA-2 appears to be an important contributor to thyrotroph development (15). Mature thyrotrophs also suppress GH production(8). This family of cells is thought to maintain fluidity so that in various situations, there is transdifferentiation: somatotrophs convert to mammosomatotrophs and lactotrophs during pregnancy, and to thyrotrophs in hypothyroidism, and these are thought to be reversible transdifferentiation processes.

GH-producing somatotrophs are located in the lateral wings of the anterior pituitary and account for approximately 50% of the cell population. By light microscopy they are strongly acidophilic cells with centrally located nuclei and diffuse cytoplasmic positivity for GH (Figure 4). Electron microscopy reveals abundant rough endoplasmic reticulum, well-formed Golgi complexes and numerous large dense secretory granules. PRL-secreting lactotrophs are scattered randomly throughout the adenohypophysis; however, they can most often be found in the posterolateral aspects of the gland. In males and nulliparous females, they constitute approximately 9% of the cell population; in multiparous females, they can represent up to 31% of the adenohypophysial cells. They are usually sparsely granulated and chromophobic polygonal cells that wrap cell processes around adjacent cells (Figure 5), usually gonadotrophs; some are densely granulated and acidophilic. The ultrastructural hallmarks of lactotrophs are the elaborate rough endoplasmic reticulum arranged in parallel arrays and occasionally forming concentric structures known as “Nebenkern” formations, the prominent Golgi complexes, and the extrusion of secretory granules at the lateral cell border, a phenomenon known as “misplaced exocytosis”. Mammosomatotrophs, which produce both GH and PRL, resemble somatotrophs but contain both GH and PRL by immunohistochemistry. The often have irregular, elongated and pleomorphic large granules and they exhibit the hallmark of PRL secretion, misplaced exocytosis. Thyrotrophs, which produce TSH, represent approximately 5% of adenohypophysial cells and are most numerous in the anteromedial aspect of the gland. They are angular chromophobic cells with multiple elongated cytoplasmic processes (Figure 6). They exhibit cytoplasmic immunoreactivity for alpha-subunit and beta-TSH. By electron microscopy they are characterized by short profiles of dilated rough endoplasmic reticulum and small secretory granules that align along the plasma membrane.

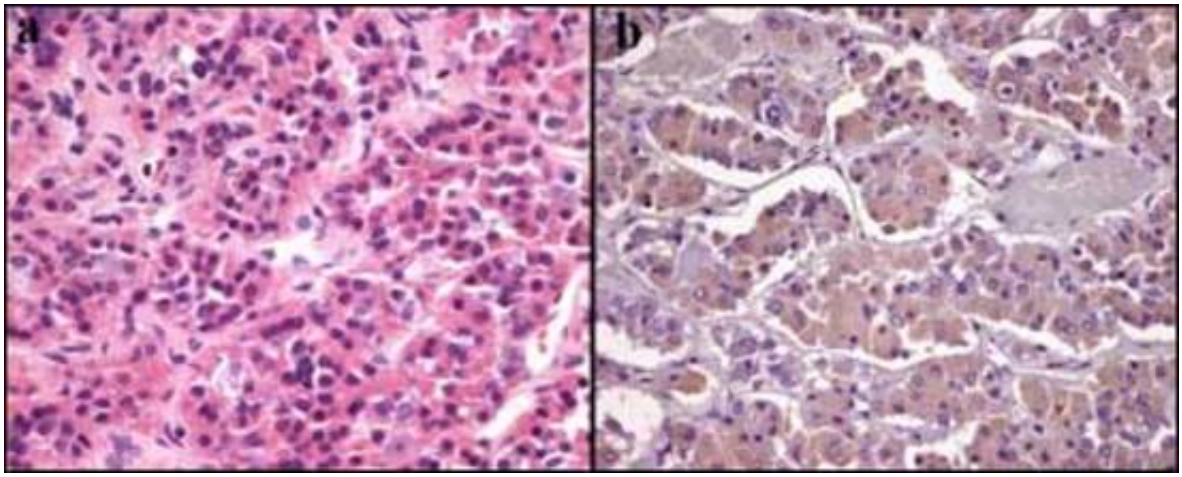

Figure 4. Somatotrophs exhibit diffuse cytoplasmic positivity for GH. They are most numerous in the lateral wings of the anterior pituitary (a) but are scattered throughout the gland including the median wedge (b).

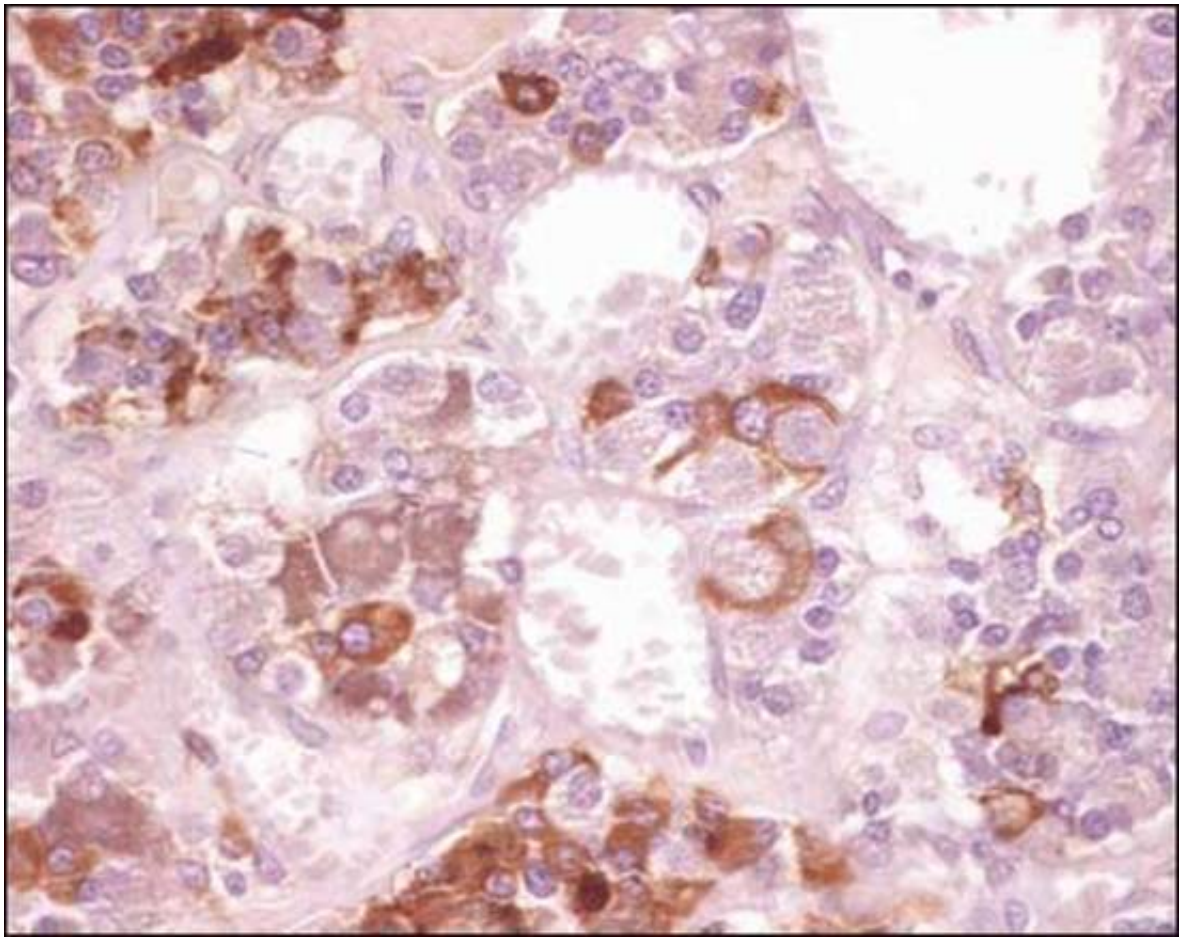

Figure 5. Lactotrophs are polygonal cells that wrap cell processes around adjacent cells, usually gonadotrophs; there is some variation in the intensity of staining for PRL.

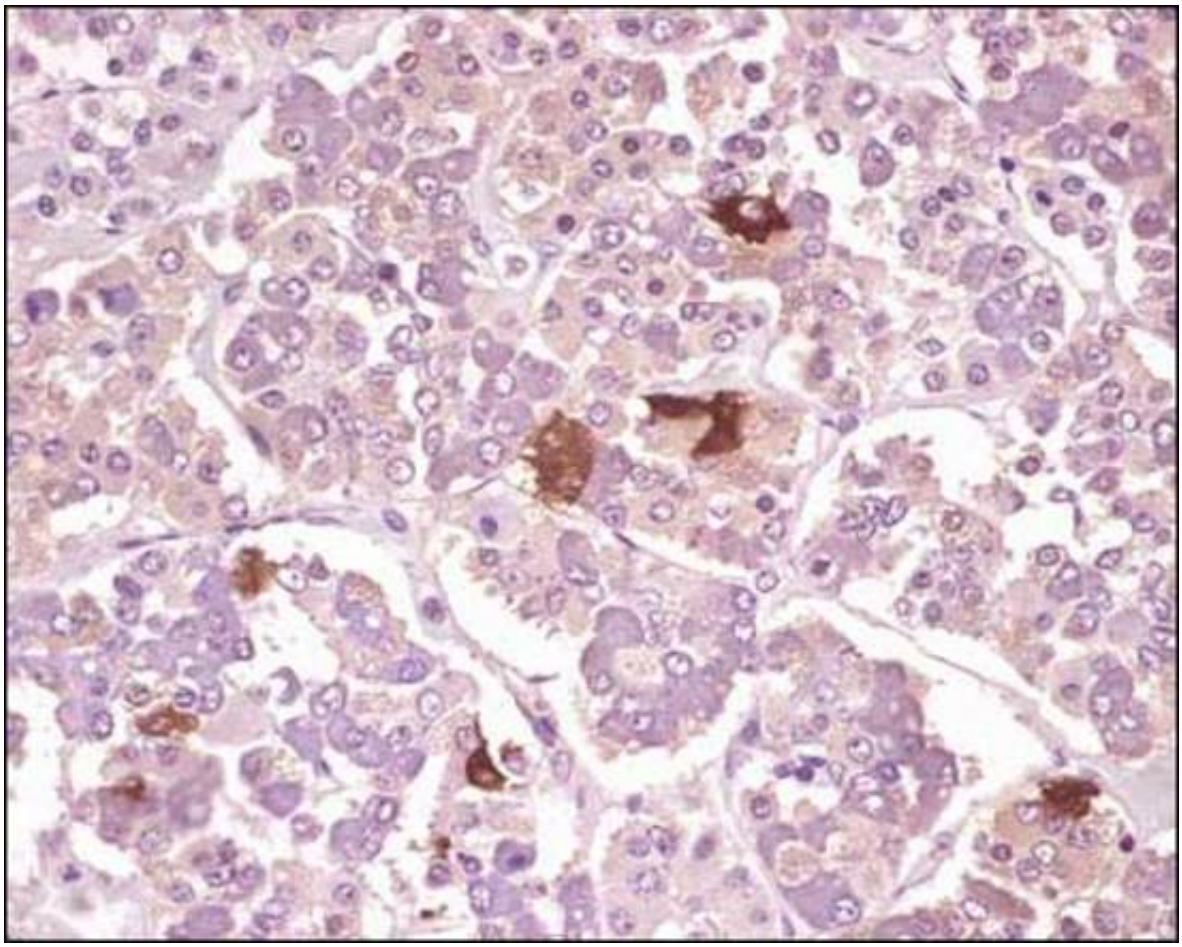

Figure 6. Thyrotrophs are angular chromophobic cells with multiple elongated cytoplasmic processes that are well seen on immunostaining for β-TSH.

Corticotrophs, which produce proopiomelanocortin (POMC) and its derivatives including adrenocorticotropin (ACTH), melanotropin (MSH) and lipotropin (LPH), represent approximately 15 to 20 percent of adenohypophysial cells. These basophilic cells (Figure 7a) have strong positivity using the periodic acid-Schiff (PAS) stain. They are concentrated mainly in the central region of the gland known as the “mucoid wedge” because of the PAS-reactivity, and are the main components of the vestigial intermediate lobe that in animals is the source of MSH (Figure 7b). In older patients they spill into the posterior lobe, a phenomenon known as “basophil invasion” (Figure 1b). They have characteristic “enigmatic bodies”, large cytoplasmic vacuoles that represent complex lysosomes (Figure 7c). The secretory granules are marked by pleomorphism of size, shape and electron density, and it is not unusual to identify indentations and evaginations of granule membranes, resulting in “heart” and “teardrop” shapes. Small bundles of intermediate filaments identified throughout the cytoplasm by electron microscopy represent keratin filaments. When corticotrophs are exposed to excess glucocorticoids, they undergo a reversible morphologic modification known as Crooke’s hyaline change (Figure 8) attributable to concentric accumulations of intermediate filaments that displace the PAS-

positive, ACTH-immunoreactive secretory granules to the juxtanuclear and peripheral cytoplasm. By light microscopy, the accumulated filaments have a pale, homogenous glassy appearance and they stain for low molecular weight cytokeratins. Corticotrophs of the pars intermedia are thought to cleave POMC differently from the ACTH-producing cells of the pars distalis, and in situations of glucocorticoid excess, they do not undergo Crooke's hyaline change. The expression of proopiomelanocortin that defines corticotrophs is dependent on the T-box transcription factor Tpit, (16). Tpit interacts with Ptx1 and Corticotropin upstream transcription-binding element (CUTE) proteins, including neuroD1/beta 2 (17;18).

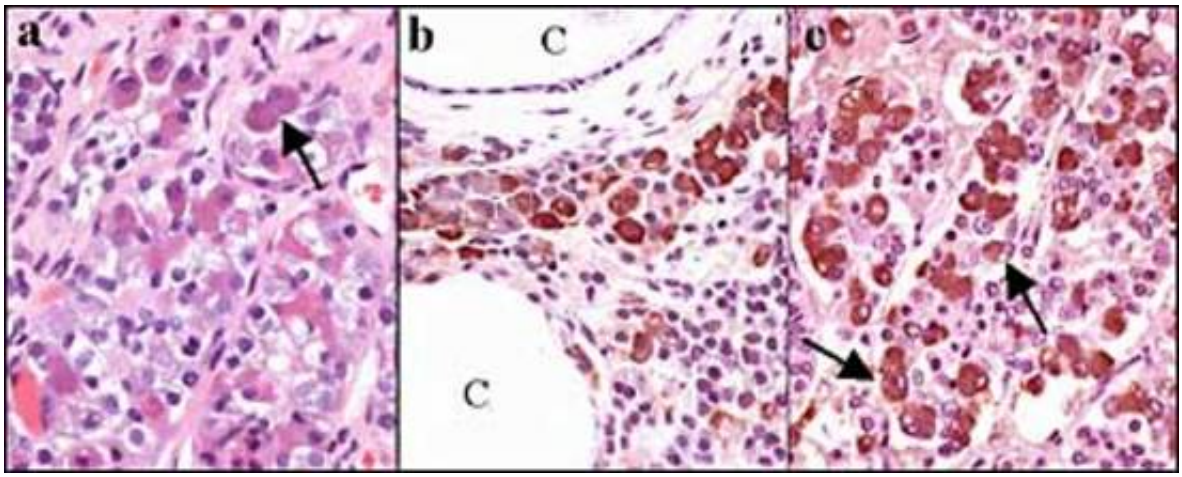

Figure 7. (a) Corticotrophs are round basophilic cells that are readily identified on H&E-stained sections. (b) They are concentrated mainly in the central region of the gland known as the "mucoid wedge" and are the main components of the vestigial intermediate lobe that is composed of small cysts (C). (c) They have characteristic "enigmatic bodies", large cytoplasmic vacuoles that represent complex lysosomes (arrows).

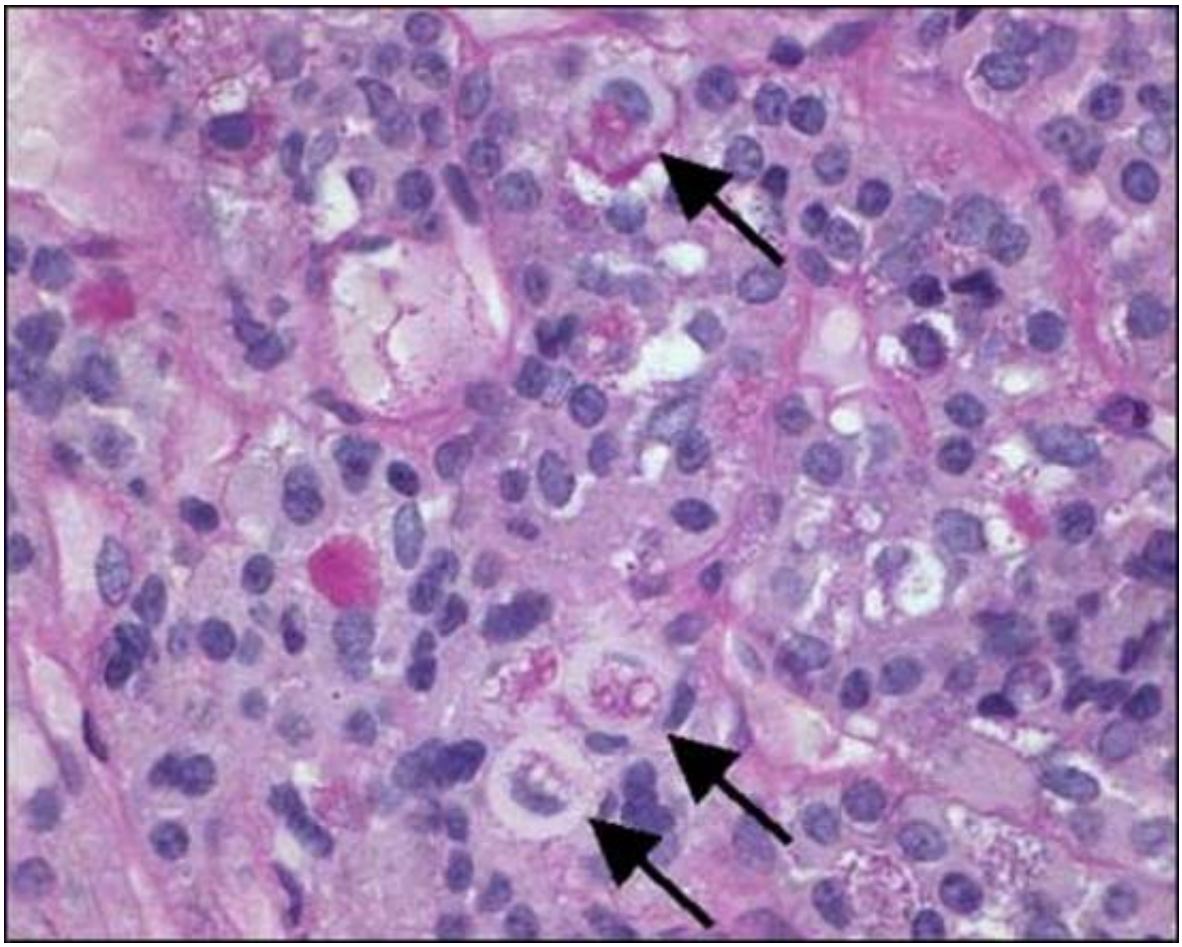

Figure 8. In situations of glucocorticoid excess, human corticotrophs (arrows) undergo accumulation of keratin filaments in the cytoplasm, resulting in a glassy hyaline appearance; the PAS-positive secretory material is trapped in the juxtanuclear region or at the plasma membrane.This is known as ‘Crooke’s hyaline change’

Expression of steroidogenic factor -1 (SF-1) (19) and GATA-2 (15) are required for gonadotroph differentiation. Gonadotrophs, which produce the two gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), account for 10% of adenohypophysial cells. They are scattered throughout the pars distalis (Figure 9) and pars tuberalis. With increasing age, these cells tend to undergo oncocytic and squamous metaplasia. These cells are reliably identified by immunoreactivity for beta-subunits of FSH and/or LH, but their ultrastructural appearance is not as characteristic as that of other adenohypophysial cells. They are oval with eccentric spherical nuclei, and their cytoplasm contains short profiles of dilated rough endoplasmic reticulum containing flocculent electron dense material. Secretory granules are generally sparse, small and scattered throughout the cytoplasm.

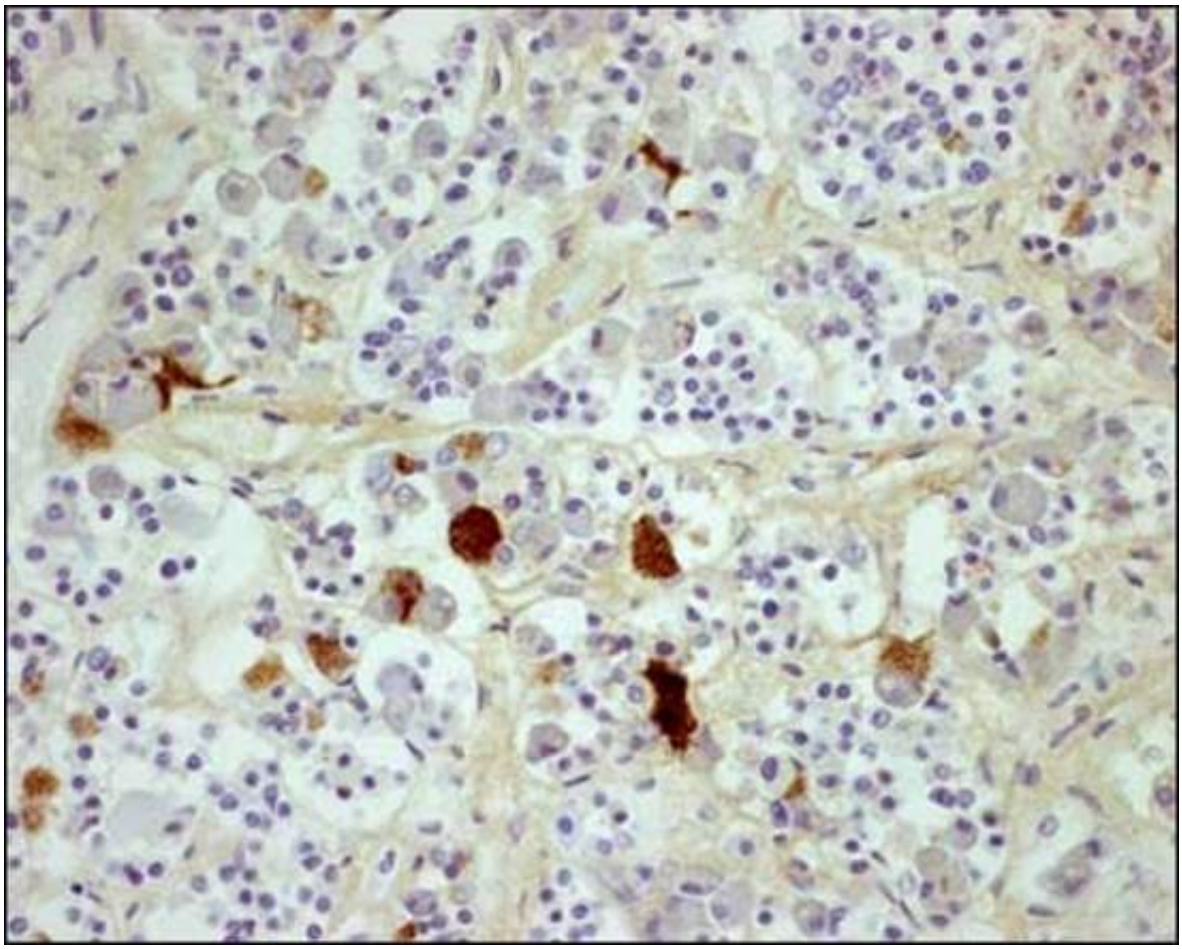

Figure 9. Gonadotrophs are scattered round to oval cells that contain strong cytoplasmic reactivity for α-subunit, β-FSH and β-LH (β-FSH shown).

The adenohypophysis includes other cells that are not hormonally active. Follicular cells form around small follicles; they are thought to derive from hormone-secreting cells in response to trauma, compression or degeneration. Folliculostellate cells are stromal sustentacular cells that surround acini of the normal gland; they are immunoreactive for S100 protein (Figure 10) or glial fibrillary acidic protein (GFAP). Scattered cells in the gland that have features of adenohypophysial hormone-secreting cells but cannot be classified are called null cells, and the normal gland also contains occasional oncocytes. These latter are characterized by accumulations of dilated, spherulated mitochondria; oncocytic change is most common in gonadotrophs and occurs rarely in other adenohypophysial cells.

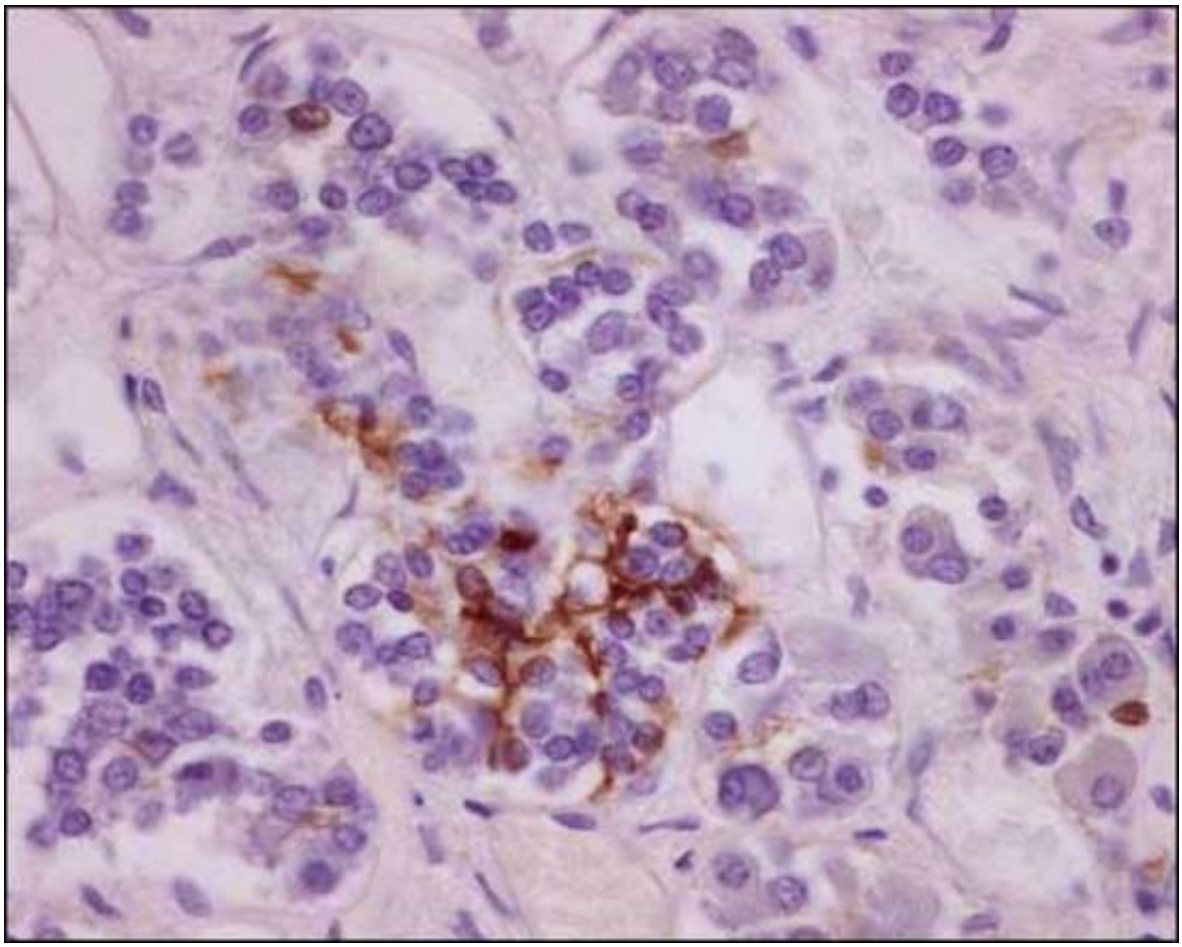

Figure 10. Folliculostellate cells are stromal sustentacular cells that surround acini of the normal gland; they are immunoreactive for S100 protein.

The pars intermedia is poorly developed in the human and is composed of small cystic spaces (Figure 1b, Figure 7b) lined by hormone-containing cells types, predominantly corticotrophs. The pars tuberalis is the superior portion of the adenohypophysis that wraps itself around the neural stalk. It is composed primarily of gonadotrophs that with age, undergo squamous metaplasia (20).

The pituitary receives its vascular supply from the superior, middle, and inferior hypophyseal arteries, all of which originate from the internal carotid arteries. The superior hypophysial arteries flow through the infundibulum of the neurohypophysis and form the portal vessels that transport regulatory hormones from the hypothalamus to the pituitary gland. The middle hypophyseal arteries supply blood directly to the adenohypophysis, while the inferior hypophyseal arteries supply the pars nervosa (21-23). Venous blood from the pituitary gland drains mainly into the internal jugular veins, however, there is evidence that reverse flow in the short portal vessels allows adenohypophysial secretion to affect neurohypophysial and hypothalamic function (24;25).

CONGENITAL AND DEVELOPMENTAL DISORDERS

ECTOPIC ADENOHYPOPHYSIS

Residual adenohypophysial tissue can be trapped anywhere along the path followed by Rathke's pouch during fetal development (26-28). The sphenoid sinus is the most common site of ectopic pituitary, followed by the immediate suprasellar region (29;30); these ectopic foci may be incidental findings, or they can undergo hyperplastic or neoplastic change.

PITUITARY APLASIA/HYPOPLASIA

These disorders are usually associated with severe congenital malformations such as those seen in the Cornelia de Lange syndrome(31)or Arnold-Chiari malformation(32). They result in hypopituitarism with subsequent thyroid and adrenal hypoplasia or aplasia(33-37). At least one form of this disorder associated with septo-optic dysplasia has been attributed to a mutation of the Rpx-1 gene (also known as Hesx-1)(38).

Inactivating mutations of PROP-1 result in combined pituitary hormone deficiency (39;40). Pituitary dwarfism with hypothyroidism occurs in patients with mutations of the pit-1 gene (41-43), likely due to hypoplasia of somatotrophs, lactotrophs and thyrotrophs (44).

PITUITARY DUPLICATION OR DYSTOPIA

These lesions are also usually associated with other congenital malformations (45;46).

EMPTY SELLA SYNDROME

A defective or absent diaphragma sella results in transmission of the pulsatile pressure waves of CSF pressure that causes sellar enlargement and flattens the pituitary against the floor of the sella turcica (47). Pituitary function is usually unaffected (48). However, some patients have hyperprolactinemia, attributed to distortion of the pituitary stalk and interference with the tonic dopaminergic inhibition of prolactin (49). This can be difficult to distinguish from prolactinoma that can also develop in the setting of empty sella.

CYSTIC LESIONS

RATHKE'S CLEFT CYSTS

Remnants of Rathke's pouch commonly form small cysts (<5mm) in the vestigial pars intermedia. These small cysts occasionally enlarge into true Rathke's cleft cysts, lined by ciliated cuboidal or columnar epithelium with occasional goblet cells (Figure 11) and areas of squamous metaplasia; as they enlarge they become symptomatic. Although this condition may occasionally be seen in children, it is most common in adults.

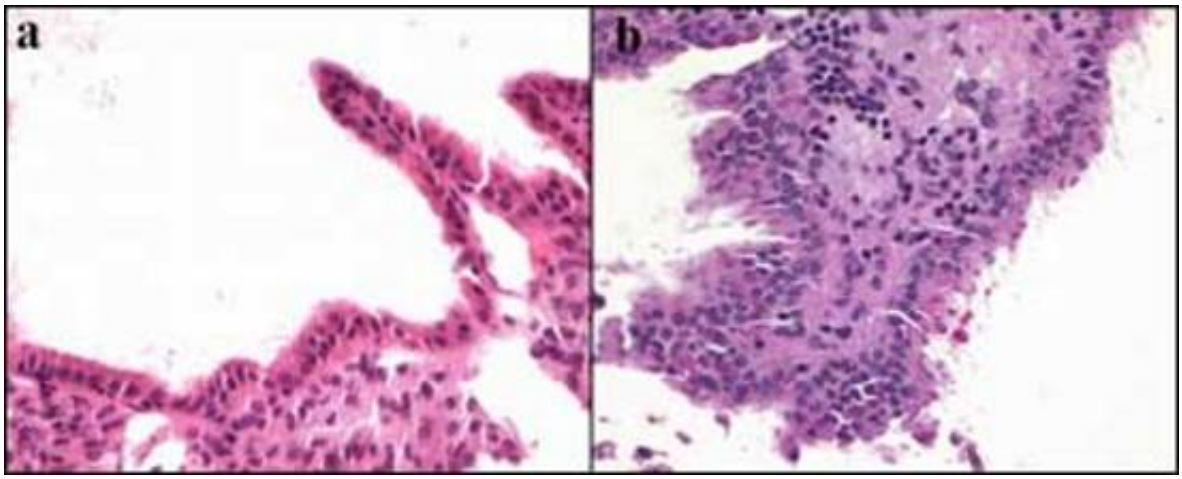

Figure 11. Rathke's cleft cysts are lined by ciliated cuboidal or columnar epithelium (a) with occasional goblet cells that stain with the PAS technique (b).

These cysts are non-functional, but may cause hypopituitarism or diabetes insipidus by compression of surrounding structures (50). Suprasellar extension may give rise to mass effects such as visual field defects and headaches. Severe cases can lead to hydrocephalus, aseptic meningitis, and rarely, abscess formation (51). CT scans usually reveal low-density cystic areas with peripheral enhancement; MRI findings tend to be more variable (52).

Treatment by drainage with or without surgical excision usually results in resolution of mass effects; however, hypopituitarism and diabetes insipidus may persist, requiring permanent hormone replacement. Recurrence rates are low.

ARACHNOID CYSTS

Arachnoid cysts originate in the arachnoid of the sellar and parasellar areas; they may be congenital or acquired. They contain clear fluid and the cyst wall is arachnoid laminar connective tissue with incomplete simple flattened epithelium.

Clinically, they can present with mass effects from suprasellar extension, or hypopituitarism and/or diabetes insipidus due to pituitary compression (50). Treatment involves drainage of cyst contents with partial surgical excision.

DERMOID AND EPIDERMOID CYSTS

Dermoid and epidermoid cysts (also known as "cholesteatomas") originate from ectopic or traumatically implanted epithelial cells. Epidermoid cysts have a lining composed of keratinizing squamous epithelium; the lining of dermoid cysts contains skin appendages such as hair follicles and sweat glands. In addition to the sellar and suprasellar regions, these cysts are also

found intracranially, most often at the cerebellopontine angle (53).

Clinical manifestations include hypopituitarism, hyperprolactinemia due to stalk compression, visual field defects, and a variety of nonspecific neurologic symptoms. Radiologic evaluation reveals a cystic lesion.

Surgical resection is usually curative. Complications include rupture of the cyst with subsequent meningitis, or the development of squamous cell carcinoma (54;55).

INFLAMMATORY DISORDERS

Inflammatory conditions can cause mass effects and/or hypothalamic-hypophysial dysfunction. Primary or idiopathic inflammatory conditions include lymphocytic hypophysitis, granulomatous hypophysitis, and xanthomatous hypophysitis(56). Secondary inflammatory conditions affecting the pituitary gland include infections and various systemic diseases.

LYMPHOCYTIC HYPOPHYSITIS

This chronic inflammatory condition of the pituitary gland is seen most commonly in young postpartum or pregnant females (57). The disorder is much less common in males; the female to male ratio is 8.5: 1. The mean ages of presentation are 34.5 years in females and 44.7 years in males. An autoimmune etiology has been proposed as the basis for lymphocytic hypophysitis due to its association with a number of other autoimmune endocrine disorders such as thyroiditis, adrenalitis, atrophic gastritis, and lymphocytic parathyroiditis and there is evidence for pituitary antibodies in patients with this disease (58). Recent data suggest that the precipitating antigen is alpha-enolase, a protein that is expressed by the placenta as well as pituitary, possibly explaining pregnancy as an initiating event.

The symptoms and signs of lymphocytic hypophysitis tend to be nonspecific, mimicking adenoma. The most common manifestation is mild to moderate hyperprolactinemia. Occasionally patients have isolated ACTH deficiency; other hormone deficiencies are rare. In addition, it can present with mass effects such as headache and visual field deficits. Rarely, patients present with isolated diabetes insipidus and the inflammatory process is restricted to the posterior lobe and stalk, which can exhibit localized enlargement; this disorder has been named infundibular neurohypophysitis (59-61).

Radiologic findings can mimic features of an adenoma; the gland is enlarged and may even exhibit suprasellar extension. However, careful MRI examination with contrast enhancement documents diffuse involvement of the gland without discrete delineation and lacking enhancement in normal gland.

At surgery the gland is inflamed, enlarged and soft or may appear atrophic and fibrotic. Microscopic examination reveals a diffuse inflammatory infiltrate composed mainly of lymphocytes and plasma cells forming occasional lymphoid follicles (Figure 12). There is destruction of the adenohypophysial tissue; the remaining parenchymal cells exhibit variable

oncocytic change. Rarely, there seems to be preferential destruction of one hormone-containing cell type. The extent of fibrosis varies with the duration of the disease.

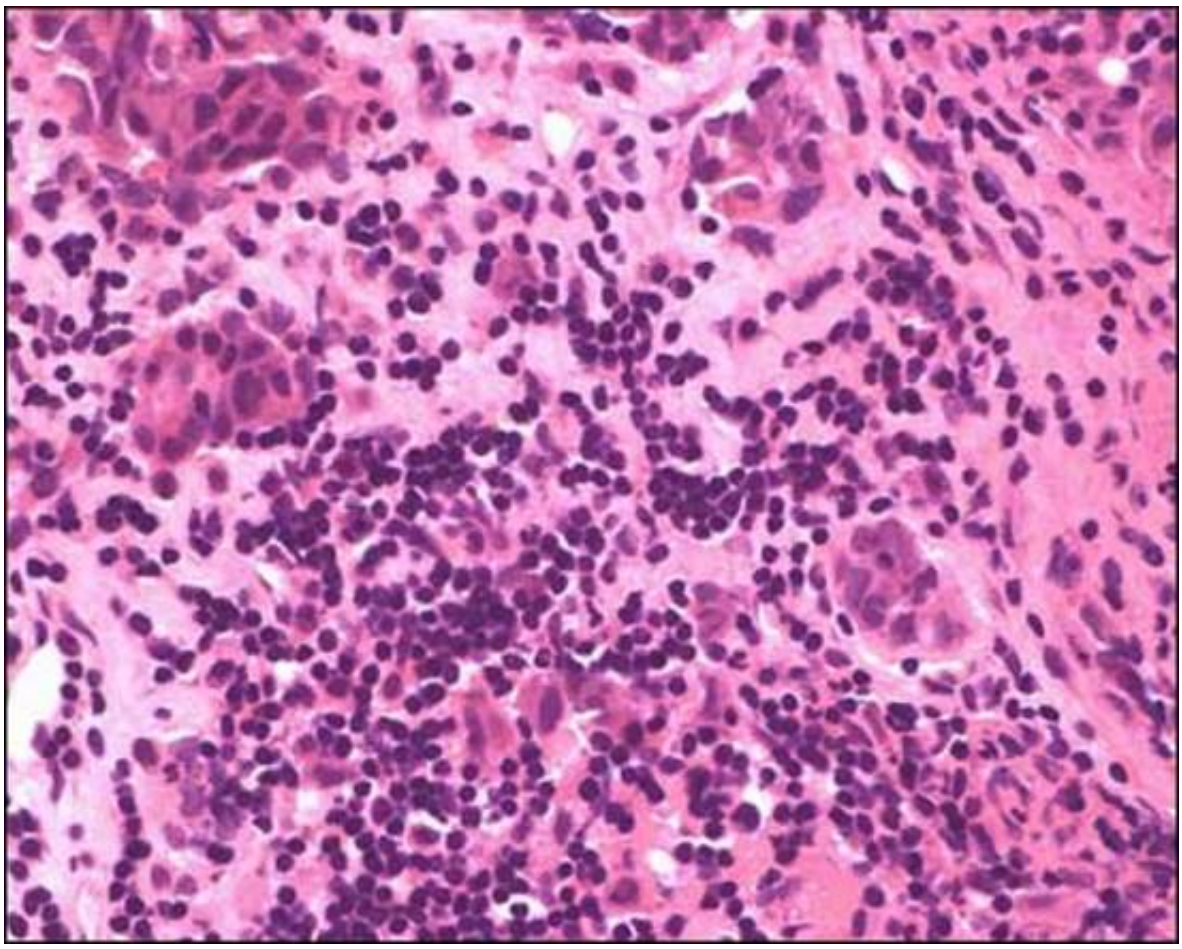

Figure 12. Lymphocytic Hypophysitis is characterized by a diffuse inflammatory infiltrate composed mainly of lymphocytes and plasma cells forming occasional lymphoid follicles. The inflammatory cells surround and destroy parenchymal cells that occasionally show oncocytic change.

The natural history of untreated lymphocytic hypophysitis is variable; it may result in permanent hypopituitarism due to extensive destruction of adenohypophysial cells, or it may run a self-limited course followed by a full recovery. Treatment for this condition is supportive with appropriate hormone replacement. Corticosteroids have been proposed to decrease inflammation, but the efficacy of this treatment has yet to be determined. Transsphenoidal surgery should be considered if the patient suffers progressive mass effects, or deterioration as evidenced by radiologic or neurologic changes. Surgical biopsy may be required to establish the diagnosis. It should be noted however, that surgery has resulted in deleterious effects in occasional case reports.

GRANULOMATOUS HYPOPHYSITIS

Idiopathic granulomatous hypophysitis is a rare chronic inflammatory disorder of unknown pathogenesis first described in 1917 (62-65). It represents one percent of all pituitary disorders with an annual incidence of 1 in 10 million. As of 1991, only 31 cases were described in publications, 21 from autopsy material. Unlike lymphocytic hypophysitis, there is no gender predilection. The mean age of presentation in females is 21.5 years; in males it is 50 years.

Patients may present with visual field deficits, cranial nerve palsies, or headaches, which may be accompanied by nausea and vomiting; this is in contrast to headaches caused by adenomas that are not associated with nausea and vomiting (66;67). Other clinical manifestations include variable degrees of adenohypophysial failure (68), hyperprolactinemia (69), diabetes insipidus, and meningitis with CSF leucocytosis (70).

Radiologic evaluation usually reveals an intrasellar mass with or without suprasellar extension (67). Sometimes, a tongue-like extension along the basal hypothalamus can be seen. Microscopically, this condition is characterized by collections of histiocytes with scattered lymphocytes and plasma cells; multinucleated giant cells may be present (Figure 13). By definition, a diagnosis of granulomatous hypophysitis cannot be made until systemic granulomatous disease has been excluded.

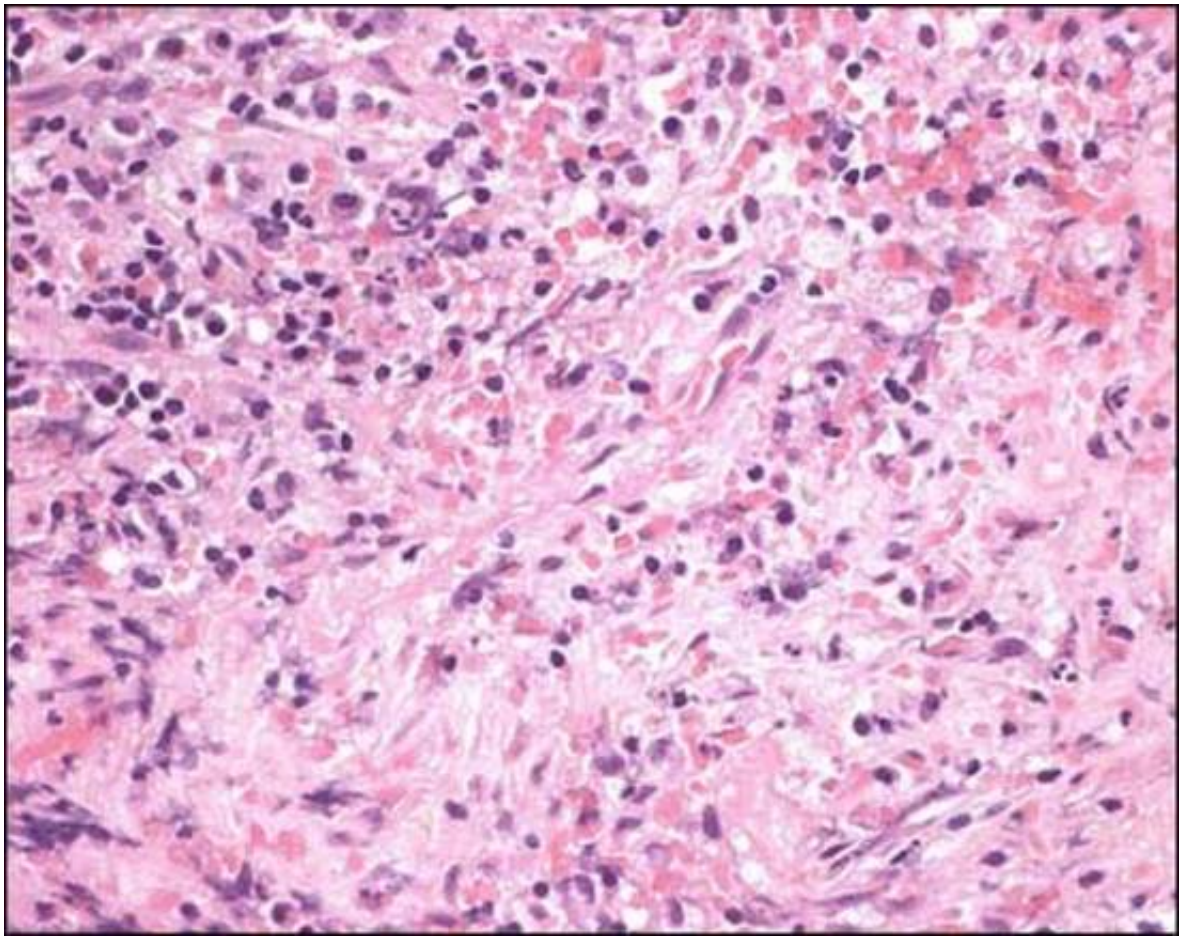

Figure 13. Granulomatous hypophysitis is characterized by collections of histiocytes with scattered lymphocytes and plasma cells; occasional giant cells and areas of necrosis mey be seen but are not identified in this area.

Treatment is somewhat controversial; transphenoidal biopsy/resection with subsequent administration of corticosteroids has been proposed (56;71).

XANTHOMATOUS HYPOPHYSITIS

This relatively new clinicopathologic entity is characterized by a chronic inflammatory infiltrate composed mainly of foamy histiocytes with scattered lymphocytes and plasma cells. The patients reported have been young females. Clinical presentation included headache, nausea, menstrual irregularity, and diabetes insipidus. One patient has had elevated prolactin levels. In most patients, a preoperative diagnosis of pituitary adenoma was suspected based on the presence of a localized lesion in the pituitary (56;72). Histologically, the condition is characterized by infiltration of the adenohypophysis by foamy lipid-containing histiocytes with areas of granulation tissue. This disorder may represent a reactive process (56), however, it remains idiopathic. A diagnosis of xanthomatous hypophysitis can only be made after causes of secondary hypophysitis are ruled out.

SECONDARY HYPOPHYSITIS

These are inflammatory lesions of the pituitary gland, which have a definite etiology (73) or occur as part of a systemic process. A number of infectious agents can involve the pituitary, including fungi, mycobacteria, brucellosis, and syphilis (74). They can result in acute or chronic hypophysitis with occasional abscess formation. Other causes of secondary hypophysitis include sarcoidosis (75), vasculitides such as Takayasu’s Disease (76) and Wegener’s granulomatosis (77), Crohn’s disease (78), Whipple’s disease, ruptured Rathke’s cleft cyst (79;80), necrotizing adenoma (73), and meningitis (70).

The acquired immunodeficiency syndrome (AIDS) may involve the pituitary gland (81). The involvement is usually infectious in nature and results in acute or chronic inflammation with necrosis. The pathogens are generally opportunistic organisms including PCP, toxoplasma gondii, and CMV.

VASCULAR DISORDERS

PITUITARY INFARCTION

Ischemic necrosis of the pituitary can result from a number of insults including head injury, hemorrhagic shock, disseminated intravascular coagulation, thrombocytopenia, and stroke

(82-85). Two unique conditions that result in pituitary infarction are Sheehan's syndrome and pituitary apoplexy.

SHEEHAN'S SYNDROME

Sheehan's syndrome is postpartum necrosis of the pituitary gland. This disorder is usually related to hypotension caused by postpartum hemorrhage (86). There is usually extensive central necrosis of the gland with a rim of viable cells at the periphery, but various degrees of necrosis can occur. Clinical manifestations appear only with significant tissue destruction. The neurohypophysis, with its independent blood supply, is usually spared.

PITUITARY APOPLEXY

This condition constitutes a true endocrine emergency in which acute hemorrhagic infarction of a sellar tumor (usually an adenoma), results in rapid expansion with symptoms and signs of elevated intracranial pressure (87). Factors predisposing to pituitary apoplexy include carotid angiography, radiation therapy, trauma, coagulopathy, temporal arteritis, diabetes mellitus, and atherosclerosis but none of these may be present.

Histologic examination reveals extensive infarction and hemorrhage. These features are common as focal changes in many pituitary tumors, however, true pituitary apoplexy refers to those extreme cases where hemorrhagic infarction of the pituitary is accompanied by the appropriate clinical features.

METABOLIC DISORDERS

AMYLOIDISIS

Amyloid deposition involving the pituitary usually occurs as part of a systemic disorder but is occasionally seen in pituitary adenomas, most commonly prolactinomas (88-92). The amyloid is deposited either in vessel walls or the interstitium, where it is an extracellular, amorphous, eosinophilic substance that stains with Congo Red and exhibits characteristic apple-green birefringence under polarized light.

HEMOSIDEROSIS

Deposition of iron occurs in the pituitary glands of patients with hemochromatosis; there is preferential deposition in gonadotrophs (93;94).

HYPERPLASIA

Hyperplasia is an increase in the number of cells of an organ or tissue in response to a stimulus. Any cell population within the pituitary gland can undergo hyperplasia. This process can be physiological or pathological (3;95;96) and when prolonged may progress to adenoma formation

(97-102).

Somatotroph hyperplasia is seen in patients with ectopic production of GH-releasing hormone (GRH) by pheochromocytomas, endocrine tumors of lung, pancreas or other elements of the dispersed endocrine system (97;103;104). Rarely, it may be associated with a gangliocytoma of the hypothalamus (105). Mammosomatotroph hyperplasia is the characteristic pituitary lesion in McCune-Albright syndrome (106;107); rarely, it may be due to GRH excess or it may be idiopathic (108). Lactotroph hyperplasia is physiologic during pregnancy or other conditions of estrogen excess, but pathological idiopathic lactotroph hyperplasia is a rare cause of hyperprolactinemia (109;110). Corticotroph hyperplasia is a cause of Cushing's disease that may be associated with a corticotroph adenoma (98-100). In rare patients, it is attributed to ectopic or eutopic excess of corticotropin-releasing hormone (CRH). It is also physiological in patients with untreated Addison's disease. Thyrotroph hyperplasia develops in patients with prolonged primary hypothyroidism(111-113). Gonadotroph hyperplasia is seen in patients with prolonged primary hypogonadism (101;102).

Radiologic evaluation of patents with hyperplasia usually reveals diffuse sellar enlargement without enhancing normal tissue on contrast administration. Hyperplasia is usually reversible if the underlying condition is appropriately treated. However, in patients with idiopathic hyperplasia, the underlying stimulus is not known. Patients with lactotroph hyperplasia can be treated with dopaminergic agonists. Those with Cushing's syndrome may require total hypophysectomy to achieve clinical control.

The key to distinguishing adenohypophysial hyperplasia from adenoma lies in the reticulin stain (Figure 14). Hyperplasia is characterized by expanded acini with an intact reticulin framework whereas adenomas have breakdown of the reticulin fiber network. Immunohistochemistry shows predominance of the hyperplastic cell type with other hormone-containing cells interspersed. Ultrastructural examination is not a reliable method to distinguish hyperplasia from adenoma, however, it was the method used to describe the cell enlargement that defines "thyroidectomy" cells (Figure 15) in patients with primary hypothyroidism, and "gonadectomy" cells in patients with primary hypogonadism. In both situations, the target cells develop abundant vacuolated cytoplasm that is occupied almost entirely by dilated rough endoplasmic reticulum with secretory material.

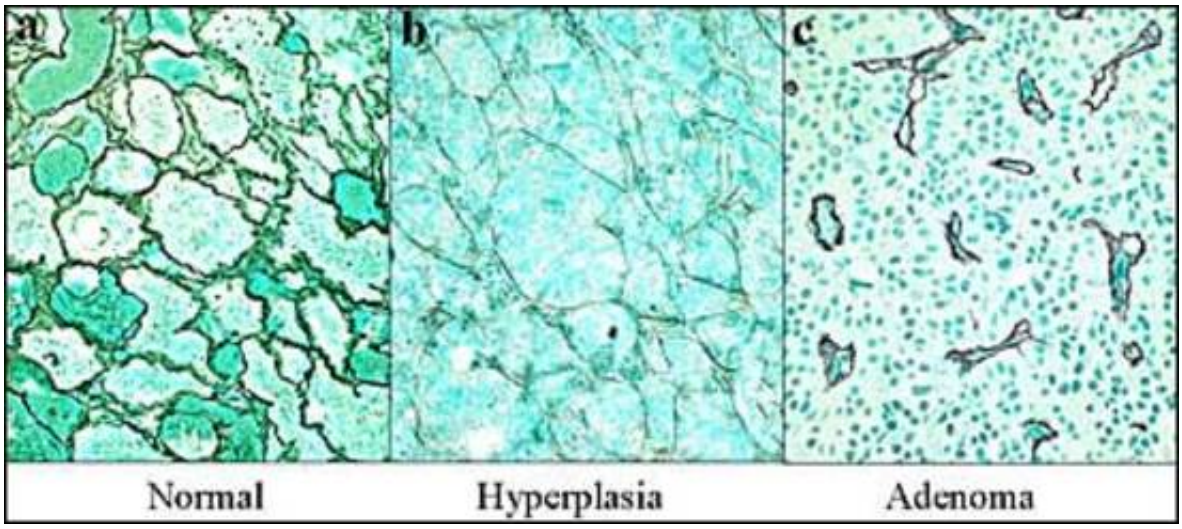

Figure 14. The reticulin stain is the most valuable tool to distinguish normal acinar architecture (a) from the expanded acini of hyperplasia (b) and to confirm total breakdown of the reticulin fiber network in adenomas (c).

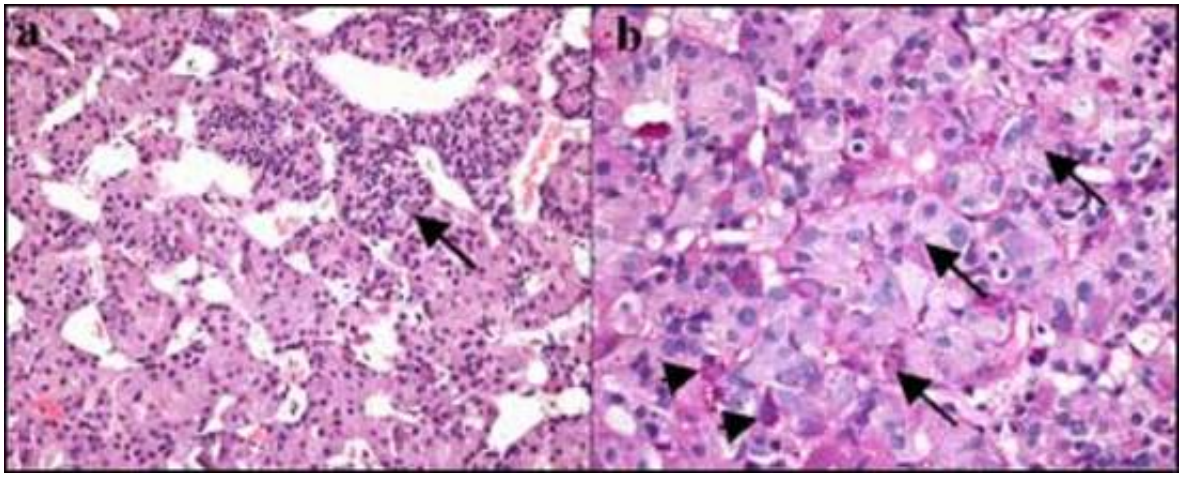

Figure 15. (a) Thyrotroph hyperplasia in a patient with primary hypothyroidism retains acinar architecture but the expanded acini are dominated by large cells with pale cytoplasm; a few smaller acidophils and basophils are identified (arrow). (b) The large “thyroidectomy” cells have abundant cytoplasm with scattered PAS-positive globules (large arrows); the PAS stain also identifies corticotrophs (short arrows).

PRIMARY TUMORS OF ADENOHYPOPHYSEAL CELLS

Primary tumors of the adenohypophysis include pituitary adenomas and the rare malignant

pituitary carcinoma. Pituitary adenomas are benign neoplasms that arise from adenohypophysial cells and represent up to 25% of all intracranial tumors (3). They are present in approximately 17% of the general population (3, 114). Their prevalence increases with advancing age; both sexes are affected equally.

The cause of sporadic pituitary adenomas is not known, however, there has been significant investigation that has shed light on some of the molecular pathogenetic events associated with pituitary neoplasia (115,116). A minority of these lesions is associated with Multiple Endocrine Neoplasia (MEN) syndromes, familial disorders in which several endocrine glands develop neoplasms or hyperplasias (117). Pituitary adenomas are most commonly associated with MEN-1 (Wermer's syndrome), an autosomal dominant disorder with incomplete penetrance (117). This syndrome is characterized by the development of parathyroid hyperplasia or adenoma, pancreatic endocrine cell hyperplasia, dysplasia and tumor, and pituitary adenoma. The various tumors develop at different times rather than synchronously in individual patients and in no specific order. Approximately two-thirds of affected patients develop a pituitary adenoma, most often producing prolactin and/or GH (118). This disease results from a germline mutation of the MEN 1 gene on chromosome 11q13 that encodes the tumor suppressor protein "menin" (115,116). Loss of heterozygosity of the intact allele is responsible for subsequent tumor formation. However, alterations of menin are not found in the more common sporadic adenomas. A number of etiologic factors have been implicated, including genetic events, hormonal stimulation and growth factors (6,115,116) and it is likely that all of these interact to initiate transformation and promote tumor cell proliferation.

Ectopic pituitary adenomas can arise in embryonic remnants of Rathke's cleft that are found in extrasellar locations including the sphenoid sinus, parapharyngeal area, suprasellar regions, middle nasal meatus, petrous temporal bone, clivus, hypothalamus, and third ventricle (119-127). Epidemiologically, these tumors resemble their intrasellar counterparts. Compared to intrasellar pituitary adenomas, higher proportions of ectopic adenomas are functional with the most common clinical presentation being Cushing's disease. Silent ectopic adenomas usually present with mass effects and their diagnosis depends on careful examination of resected tissue specimens.

CLASSIFICATION OF PITUITARY ADENOMAS

There are several classification schemes for pituitary adenomas: functional, anatomic/radiologic, histologic, immunohistochemical, ultrastructural, and clinicopathologic (3).

The functional classification is used clinically. It groups adenomas according to the hormonal syndromes with which they are associated. This includes the various functioning adenomas and the clinically "silent" or nonfunctioning adenomas.

The anatomic/radiologic classification categorizes pituitary adenomas based on size and degree of invasion (128). Sellar enlargement can be demonstrated in most patients with CT scan but MRI is the imaging technique of choice to identify a pituitary adenoma and delineate residual normal tissue that enhances with contrast more readily than tumor tissue.

The histologic classification, based on histochemical stains, divides adenomas into those that are acidophilic, basophilic, and chromophobic. This classification is of limited value and has largely been abandoned.

The immunohistochemical classification categorizes pituitary adenomas based primarily on hormone content with additional information provided by immunoreactivity for transcription factors and keratins (3).

Although electron microscopy can be extremely valuable in the diagnosis of certain tumors, the ultrastructural classification of adenomas is less commonly utilized.

The clinicopathologic classification represents the most effective classification scheme (3,129). It categorizes adenomas using both morphologic and clinical features as shown in Table 1.

Table 1. Clinicopathological Classification of Pituitary Adenomas

Functioning Adenomas	Nonfunctioning Adenomas
GH-PRL-TSH Family	
Adenomas causing GH-excess 1. Densely granulated somatotroph adenomas 2. Sparsely granulated somatotroph adenomas 3. Mammosomatotroph adenomas	Silent lactotroph adenomas
Adenomas causing hyperprolactinemia 1. Lactotroph adenomas 2. Acidophil stam cell adenomas	Silent lactotroph adenomas
Adenomas causing TSH excess 1. Thyrotroph adenomas	Silent thyrotroph adenomas
ACTH Family	
Adenomas causing ACTH excess 1. Densely granulated corticotroph adenomas 2. Sparsely granulated corticotroph adenomas	Silent corticotroph adenomas
Gonadotroph Family	
Adenomas causing gonadotropin excess 1. Gonadotroph adenomas	Silent gonadotroph adenomas (null cell adenomas, oncocytomas)
Unclassified Adenomas	
1. Unusual plurihormonal adenomas	Immunonegative adenomas

FUNCTIONING SOMATOTROPH ADENOMAS

Somatotroph adenomas arise from GH-producing cells and represent 10 to 15% of pituitary adenomas. GH excess in adults manifests as acromegaly, and gigantism results from excessive GH prior to epiphyseal plate closure (130). The details of clinical and biochemical parameters of acromegaly and gigantism are covered elsewhere in this text. Hyperprolactinemia can be prominent in some patients; this may be the result of stalk compression in macroadenomas, or the elaboration of PRL in addition to GH by the tumor.

Grossly, these tumors are usually well demarcated and are located in the lateral wing of the adenohypophysis. Microscopically, there are several subtypes of somatotroph adenomas.

Densely Granulated Somatotroph Adenomas are composed of acidophilic cells arranged in a trabecular, sinusoidal, or diffuse architecture (Figure 16). The tumor cells show strong, diffuse cytoplasmic immunoreactivity for GH and strong nuclear immunoreactivity for Pit-1 (3). Tumor cells exhibit moderate perinuclear positivity with antibodies to low molecular weight cytokeratins. There is variable cytoplasmic immunoreactivity for alpha-subunit of glycoprotein hormones. By electron microscopy (129), the tumor cells resemble nontumorous somatotrophs; they have spherical nuclei with prominent nucleoli. Parallel arrays of rough endoplasmic reticulum are found and Golgi complexes are well formed. The numerous secretory granules are homogeneous, dense and spherical with diameters ranging from 150 to 600 nm.

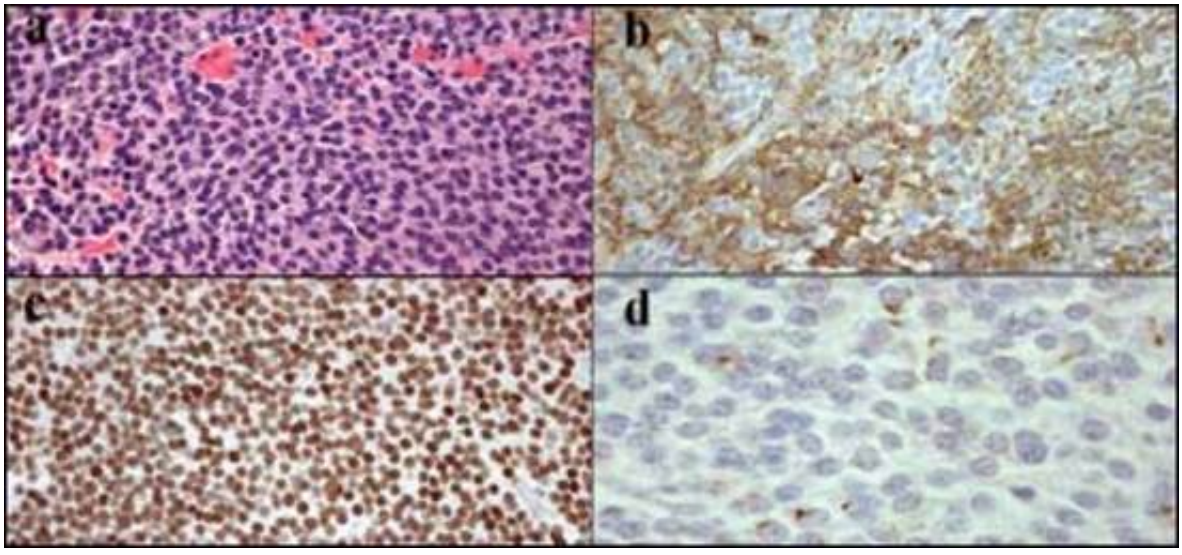

Figure 16. Densely Granulated Somatotroph Adenomas are composed of acidophilic cells arranged in a trabecular, sinusoidal, or diffuse architecture (a). The tumor cells show diffuse cytoplasmic immunoreactivity for GH (b) and strong nuclear immunoreactivity for Pit-1 (c). In contrast to the sparsely granulated variant (see keratin positivity is perinuclear and faint (d) .

Sparsely Granulated Somatotroph Adenomas are composed of solid sheets of chromophobic cells with striking nuclear pleomorphism and prominent nucleoli that can mimic metastatic carcinomas (Figure 17). Immunohistochemical stains for low molecular weight cytokeratins reveal the characteristic feature of this tumor type, the fibrous body, which manifests as juxtanuclear globular reactivity (3). There is focal, weak cytoplasmic immunoreactivity for GH and occasionally for alpha-subunit. Nuclear immunoreactivity for Pit-1 is usually present. Ultrastructurally (129), the tumor cells are irregularly shaped with eccentric, pleomorphic, and often multilobulated nuclei. The rough endoplasmic reticulum can be either poorly or well developed. The characteristic fibrous body is a juxtanuclear, spherical mass composed of intermediate filaments. Secretory granules are sparse and range in size from 100 to 250 nm.

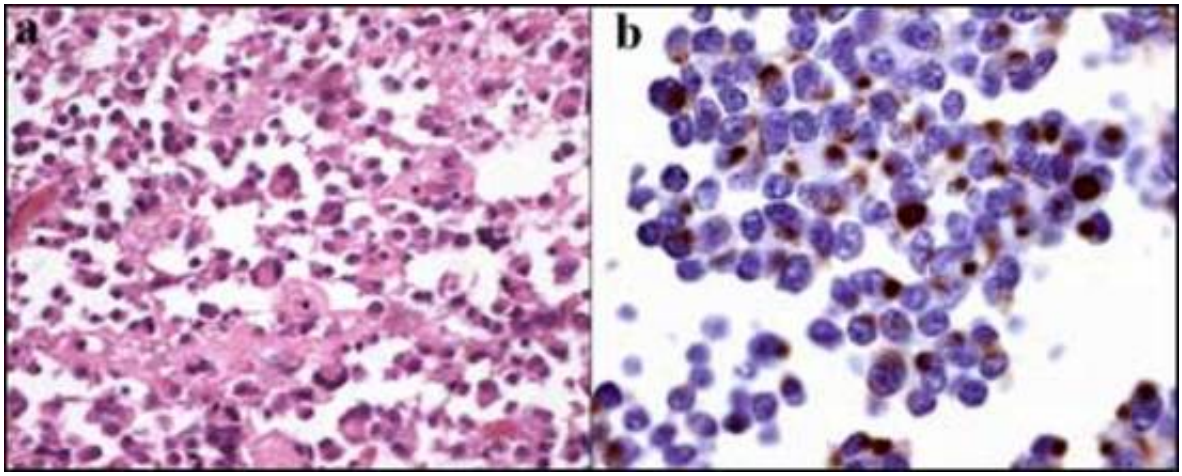

Figure 17. Sparsely Granulated Somatotroph Adenomas are composed of chromophobic cells with striking nuclear pleomorphism and prominent nucleoli that can mimic metastatic carcinoma (a). Immunohistochemical stains for low molecular weight cytokeratins reveal the characteristic feature of this tumor type, the fibrous body, which manifests as juxtanuclear globular reactivity (b).

Mammosomatotroph Adenomas produce both GH and PRL. They are associated with acromegaly and are the most frequent findings in patients with gigantism and in young patients with acromegaly. Microscopically, the tumor is composed mainly of acidophilic cells arranged in a diffuse or solid pattern. Chromophobic cells may be scattered throughout. Immunohistochemically, the tumor cells are strongly immunoreactive for GH and variably immunoreactive for alpha-subunit and PRL(3). Staining for low molecular weight cytokeratins yields a perinuclear pattern of staining similar to that of normal somatotrophs and the cells of densely granulated somatotroph adenomas. There is strong nuclear immunoreactivity for Pit-1 and occasionally for ER. Very rarely, beta-TSH can be demonstrated in the cytoplasm. Ultrastructurally, the tumor cells resemble densely granulated somatotrophs(129), however, secretory granules have mottled cores, are variably pleomorphic, and can measure up to 1000nm. In addition, the cells exhibit misplaced exocytosis, which is the classic feature of PRL secretion.

Drug Effects

These tumors rarely show a response to dopaminergic agents. Treatment with somatostatin analogues often results in inhibition of GH excess (131), most successfully in patients with densely granulated as compared with sparsely granulated tumors (132). There is, however, no consistent tumor size reduction or morphologic alteration attributable to this therapy (133).

FUNCTIONING LACTOTROPH ADENOMAS

Tumors arising from PRL-secreting adenohypophysial cells are the most common type of pituitary adenoma (134;135). Although almost half of adenomas found incidentally at autopsy are of this type (136), the incidence is much lower in surgical series, probably because these tumors are often treated medically. This tumor is more common in females, who tend to present at a younger age with hormonal disturbances. In contrast, men tend to present later, with larger tumors that more often result in mass effects and hypopituitarism secondary to adenohypophysial destruction (137). While this has traditionally been attributed to sexual dimorphism of the perception of the relevant symptoms, recent evidence suggests that the tumors grow faster in men (138). There are three variants of PRL-secreting pituitary adenomas: sparsely granulated and densely granulated lactotroph adenomas and the rare but aggressive acidophil stem cell tumor.

An elevated serum PRL level greater than 250ng/mL (5000mU/l) is virtually diagnostic of a prolactin secreting adenoma. Values less than this must be interpreted with more caution, since a number of physiologic, pharmacologic, and pathologic conditions may cause elevated serum PRL levels. Lactotroph adenomas tend to have a good correlation between tumor size and PRL level. However, this is not often true for patients with acidophil stem cell adenomas.

Microadenomas are most commonly located in the posterolateral portions of the gland. Macroadenomas may invade into dura mater, nasal sinuses, and bone. They can be soft and red, or gray and firm. Occasionally, the presence of psammoma bodies results in a gritty consistency.

Sparsely Granulated Lactotroph Adenomas are the more common variant. The chromophobic tumor cells are arranged in papillae, trabeculae, or solid sheets; tumor cells may form pseudorosettes around vascular spaces (3). Calcification with the formation of frank psammoma bodies is occasionally present. Amyloid deposition is a rare feature. The tumor cells show strong immunoreactivity for PRL in a juxtanuclear globular pattern that corresponds to the Golgi region (Figure 18). Nuclear staining for Pit-1 is usually present and estrogen receptor positivity may be found by immunohistochemistry. Ultrastructurally (129), the cells have large nuclei with prominent nucleoli. The rough endoplasmic reticulum is prominent and arranged in distinctive parallel arrays; when arranged in concentric whorls, they are known as “Nebenkern formations”. The large, well-developed Golgi complexes harbor immature pleomorphic granules. Secretory granules are spherical, sparse, and range in size from 150 to 300 nm. Misplaced exocytosis, or the expulsion of secretory granules from the lateral cell membrane into the extracellular space, is a diagnostic feature of PRL-producing tumors.

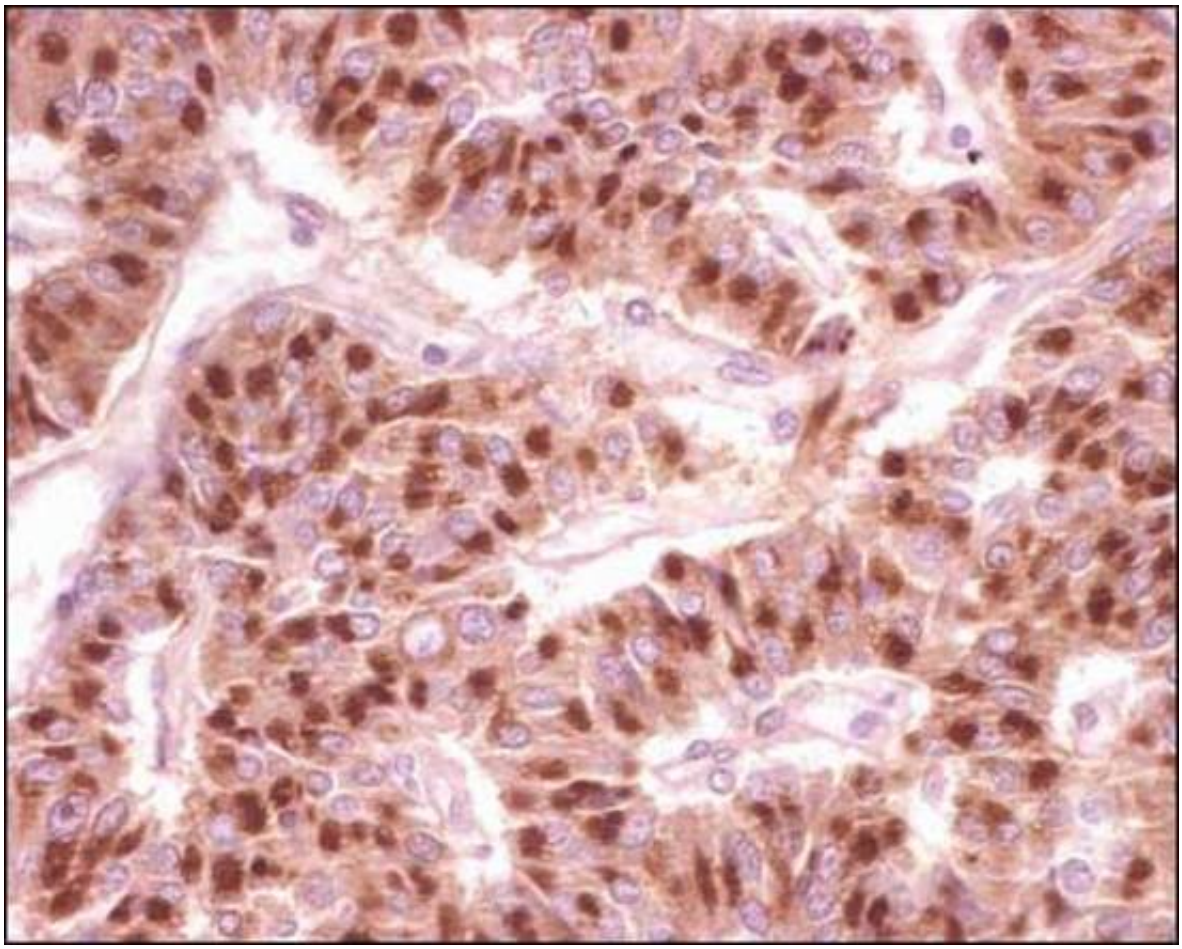

Figure 18. Sparsely Granulated Lactotroph Adenomas are characterized by strong immunoreactivity for PRL in a juxtanuclear globular pattern that corresponds to the Golgi region.

Densely Granulated Lactotroph Adenomas are much less common than the sparsely granulated variant. These tumors are composed of acidophilic cells that exhibit diffuse cytoplasmic positivity for PRL, unlike the juxtanuclear Golgi pattern seen in the sparsely granulated adenoma. Ultrastructurally, densely granulated cells have abundant rough endoplasmic reticulum; secretory granules are numerous and can measure up to 700 nm. Misplaced exocytosis is again a diagnostic feature.

The Acidophil Stem Cell Adenoma is usually composed of solid sheets of large cells that are slightly acidophilic due to the accumulation of mitochondria. Large cytoplasmic vacuoles corresponding to giant mitochondria can be easily appreciated by light microscopy (3). The classic immunohistochemical profile shows strong diffuse immunoreactivity for PRL and scant immunoreactivity for GH. Some tumors may lack detectable immunoreactivity for GH. Staining with low molecular weight cytokeratins usually allows the detection of scattered fibrous bodies (3). Electron microscopy may be necessary to render a definitive diagnosis of this tumor (129). Ultrastructurally, the cells are elongated with oval or irregular nuclei. The cytoplasm is occupied

by numerous enlarged mitochondria; distinctive giant mitochondria containing electron dense tubules are frequently seen. Fibrous bodies, or juxtanuclear bundles of cytokeratin intermediate filaments, identical to those seen in sparsely granulated somatotroph adenomas, are scattered throughout the tumor. Secretory granules are scant and range in size form 150 to 200 nm. Misplaced exocytosis can be seen.

Drug Effects. Administration of dopamine agonists such as bromocriptine results in a dramatic clinical response in patients with prolactinomas. The rapid fall in serum PRL is accompanied by an almost equally rapid reduction in tumor size that is due to tumor cell shrinkage (139). In the absence of relevant history, the changes may be a source of diagnostic confusion. The cytoplasm of the tumor cells shrinks, resulting in a marked increase in cellularity. The resulting picture can histologically resemble a lymphoma. These changes are reversible upon discontinuation of therapy; however, the alterations may be permanent in a small population of tumor cells. After chronic therapy, there is occasionally interstitial and perivascular fibrosis along with hemorrhage and hemosiderin deposition.

The acidophil stem cell adenoma is generally resistant to treatment with bromocriptine (140). Surgical resection is necessary for these aggressive tumors; careful postoperative monitoring is required, as recurrence is common. Radiation therapy may play a role in the management of recurrent acidophil stem cell tumors.

FUNCTIONING THYROTROPH ADENOMAS

Thyrotroph adenomas account for less than one percent of all pituitary neoplasms. Patients with pituitary-dependent TSH excess may exhibit features of hyperthyroidism or hypothyroidism, or may be euthyroid (141). Because most thyrotroph tumors are invasive macroadenomas, mass effects with visual field disturbances are common.Diffuse thyrotroph hyperplasia can mimic this disorder therefore thyroid function tests should be performed in all patients with elevated levels of serum TSH to exclude primary thyroid failure, and radiological evaluation with an MRI scan is essential to identify the presence of a discrete sellar tumor rather than diffuse hyperplasia.

Grossly, thyrotroph adenomas tumors tend to be invasive and fibrotic macroadenomas at the time of diagnosis.

By light microscopy, these tumors are composed of chromophobic cells with indistinct cell borders and varying degrees of nuclear pleomorphism (Figure 19). Architecturally, the tumors most commonly exhibit a solid or sinusoidal pattern. Stromal fibrosis is relatively common and occasional psammoma bodies may be present. The tumor cells show variable immunoreactivity for alpha-subunit and beta-TSH. Immunohistochemistry highlights the polygonal structure of the tumor cells that usually have elongated processes (3). Ultrastructurally, thyrotroph adenoma cells resemble normal thyrotrophs (129). The polygonal cells have euchromatic nuclei and long interdigitating cytoplasmic processes that contain abundant rough endoplasmic reticulum with prominent and spherical Golgi bodies. Secretory granules, which are spherical and range in size from 150 to 250 nm, tend to accumulate along the cell membrane. Some densely granulated tumors occasionally have larger granules measuring up to 350 nm.

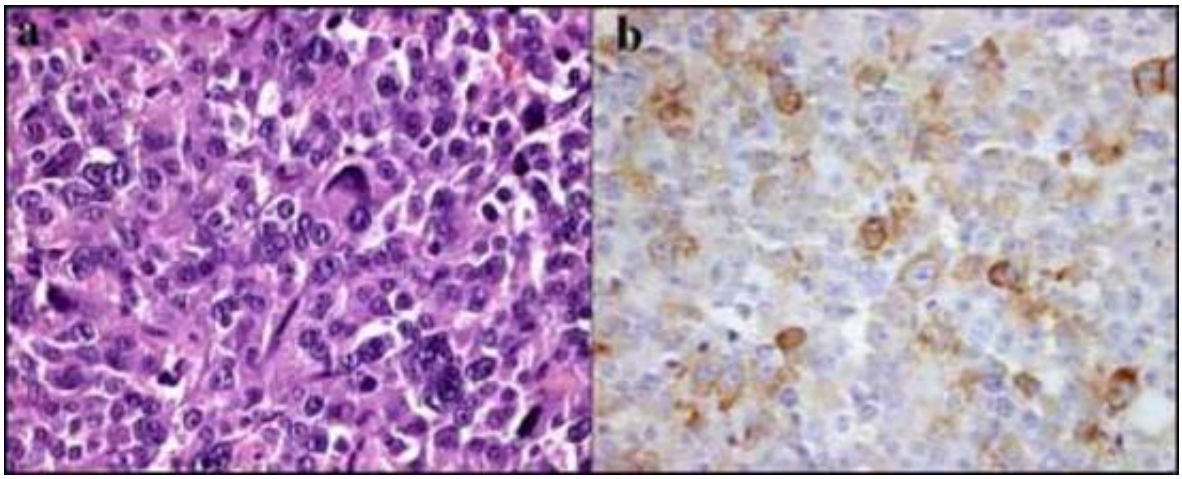

Figure 19. Thyrotroph adenomas are composed of chromophobic cells with indistinct cell borders and varying degrees of nuclear pleomorphism with hyperchromasia and marked atypia (a). Immunohistochemistry identified α-subunit and β-TSH (b) in tumor cells.

FUNCTIONING CORTICOTROPH ADENOMAS

Tumors composed of ACTH-secreting corticotrophs represent 10 to 15% of all pituitary adenomas. There are three recognized variants: densely granulated corticotroph adenomas, sparsely granulated corticotroph adenomas, and Crooke's cell adenomas. Cushing's disease, defined as pituitary-dependant hypercortisolism, has a number of clinical manifestations that are reviewed elsewhere in this text.

The most common cause of Cushing's disease is a basophilic microadenoma (3). These small tumors may be centrally located, as corticotrophs are most abundant in the median wedge of the anterior pituitary, but they usually exhibit lateralization of blood supply, justifying inferior petrosal sinus sampling. Macroadenomas are associated with Nelson's syndrome, or represent chromophobic or sparsely granulated adenomas in patients with less florid hormone excess. The possibility of corticotroph hyperplasia must be considered in the differential diagnosis of this disorder.

Densely granulated corticotroph adenomas are the most common type of corticotroph adenoma. By light microscopy, these tumors are composed of basophilic cells arranged in a sinusoidal architecture. The tumor cells exhibit cytoplasmic PAS positivity. They are immunoreactive for ACTH, beta-endorphin and other POMC-derived peptides. Positivity for low molecular weight cytokeratins is seen in patients with Cushing's disease; in patients with Nelson's syndrome, the tumor cells do not accumulate filaments of keratin. Ultrastructurally (129), corticotroph cells are large and polygonal with ovoid or irregular nuclei that harbor nucleoli in contact with the inner nuclear membrane. The cytoplasm contains prominent rough endoplasmic reticulum with abundant free ribosomes, spherical Golgi complexes and perinuclear intermediate filaments composed of cytokeratins that are prominent in patients with Cushing's syndrome but are not

conspicuous in Nelson’s syndrome. The secretory granules range in size from 150 to 450nm in diameter and are distinctive because of their marked variability in shape and electron density.

Sparsely granulated corticotroph adenomas are less common than the densely granulated variant. By light microscopy, the tumor cells are chromophobic (Figure 20) and are negative or only focally positive with the PAS stain. They exhibit strong immunoreactivity for cytokeratins and weak immunoreactivity for ACTH and other POMC-derived peptides (3). Ultrastructurally (129), the cells contain less well-developed organelles and scant secretory granules, but the characteristic variability of size, shape and density of the granules characterizes them as corticotrophs.

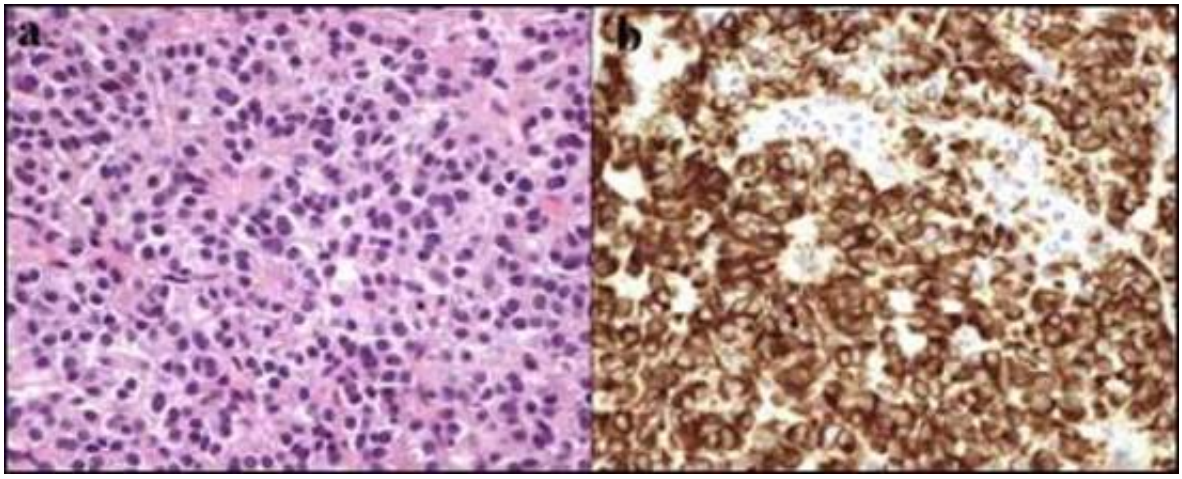

Figure 20. Corticotroph adenomas may be basophilic or chromophobic (a). They exhibit strong immunoreactivity for cytokeratins (b) and may have diffuse or focal, strong or weak immunoreactivity for ACTH and other POMC-derived peptides.

Crooke’s cell adenomas are rare tumors that exhibit Crooke’s hyaline change (142;143). Usually, Crooke’s hyalinization is restricted to nontumorous corticotrophs, but rarely this marker of feedback suppression by glucocorticoids is seen in adenomas. These tumors can be associated with Cushing’s disease, but it is generally an unusual form of the disease, such as cyclical Cushing’s. The tumor cells can exhibit marked cytologic and nuclear atypia (Figure 21). The perinuclear ring of pale hyaline material represents the accumulation of low molecular weight cytokeratin filaments that are intermediate filaments on electron microscopy (144). The cells exhibit a rim of peripheral positivity when stained with PAS, and this is due to immunohistochemically detectable ACTH in secretory granules located either at the periphery of the cell or in the perinuclear region.

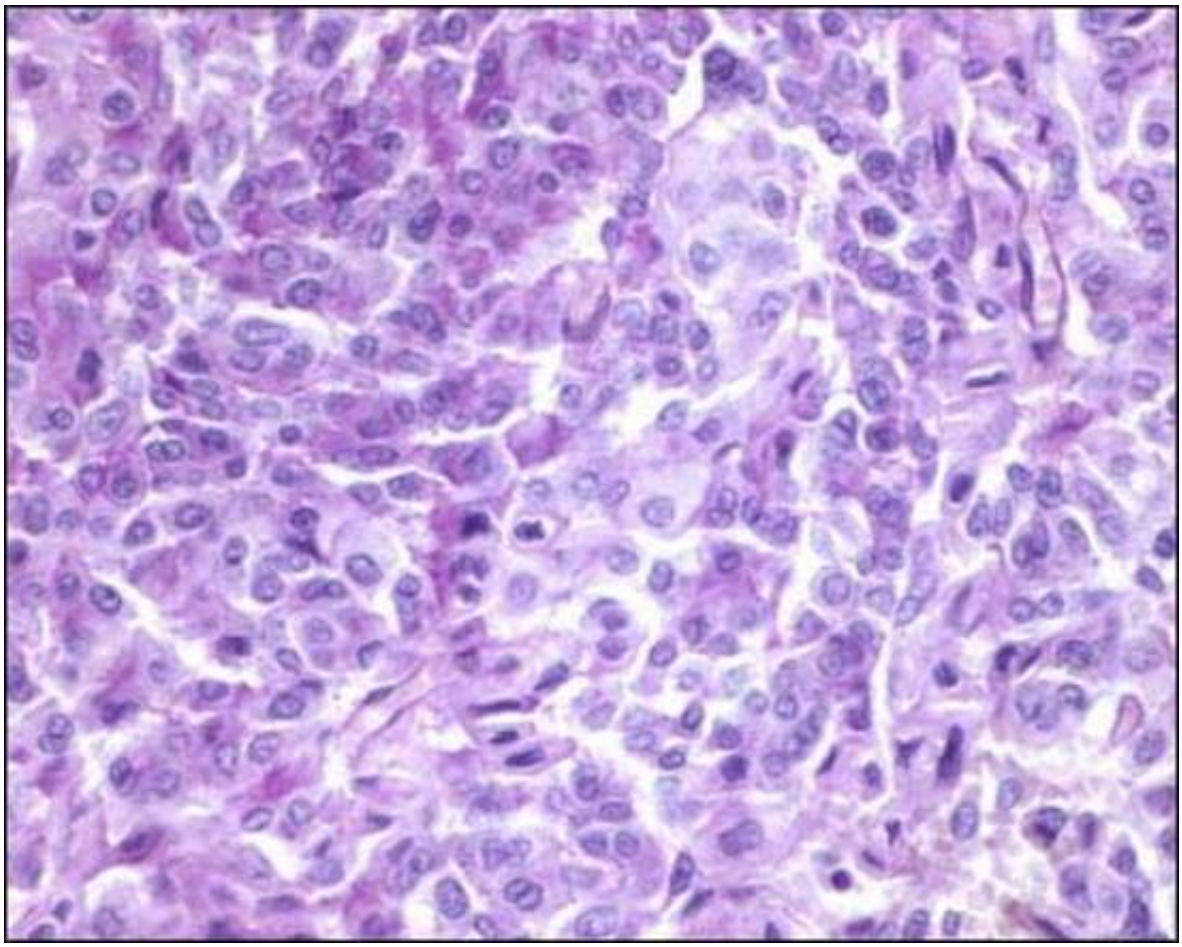

Figure 21. Crooke’s cell adenomas exhibit marked cytologic and nuclear atypia. The perinuclear ring of pale hyaline material represents the accumulation of low molecular weight cytokeratin filaments in these tumor cells.

FUNCTIONING GONADOTROPH ADENOMAS

These tumors are mainly diagnosed in middle-aged men with no prior history of gonadal dysfunction (145). Although they occur in women, the clinical diagnosis is more often missed because elevation of gonadotropins is considered to be physiological in postmenopausal women and the tumors are considered to be nonfunctional (146).

Grossly, the tumors are large, soft, well vascularized, and occasionally have foci of hemorrhage or necrosis. Microscopically, they are characterized by chromophobic cells arranged in a trabecular, papillary, or sinusoidal pattern (147). There is usually prominent pseudorosette formation around vascular spaces (Figure 22). Focal oncocytic change is quite common. Scant PAS positivity may be demonstrated in some tumor cells. The tumor cells exhibit, with variable intensity of immunoreactivity for alpha-subunit, beta-FSH, and beta-LH. As well, there is strong nuclear staining with steroidogenic factor-1 (3). It is common for gonadotroph adenomas to

exhibit ultrastructural diversity (129;148). Well-differentiated tumor cells are elongated with the nucleus occupying one pole and secretory granules accumulate at the opposite pole. Poorly differentiated cells are generally ovoid or polygonal and lack polarity. Rough endoplasmic reticulum is usually composed of short dilated profiles that contain flocculent material. Golgi bodies are perinuclear, large, and globular. Secretory granules are generally small (250nm), variable in number, and located close to the cell membrane. Cells exhibiting oncocytic change have abundant mitochondria.

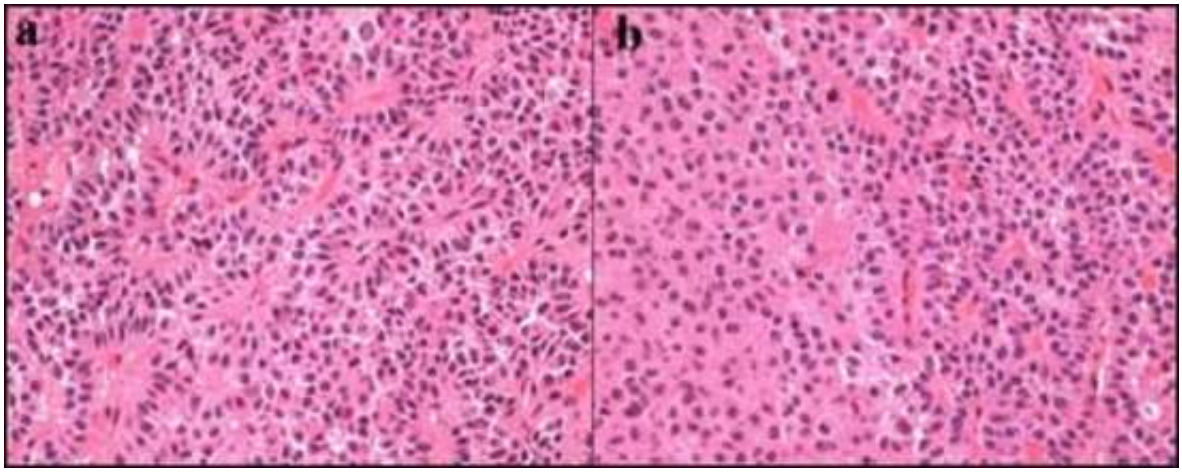

Figure 22. Gonadotroph adenomas are characterized by cuboidal to columnar chromophobic cells arranged in a trabecular, papillary, or sinusoidal pattern with prominent pseudorosette formation around vascular spaces (a). They often exhibit focal oncocytic change with nests of round to polygonal cells that have abundant granular cytoplasm (b).

CLINICALLY NON-FUNCTIONING PITUITARY ADENOMAS

These tumors account for approximately one third of all pituitary adenomas. Due to their lack of clinically detectable hormonal activity, they tend to present with mass effects such as headache, visual field deficits, cranial nerve defects, or rarely, cavernous sinus syndrome (3). If there is extensive tissue destruction, hypopituitarism results in clinical symptomatology. Less commonly, pituitary apoplexy with hemorrhage into the tumor causes a medical emergency. Patients may have varying degrees of hypopituitarism depending on the amount of adenohypophysial tissue destruction. There is no evidence of hormone excess, however, stalk compression without significant adenohypophysial destruction can result in mild hyperprolactinemia.

The diagnosis of silent pituitary adenomas is based solely on morphologic features of the tumor (3). Silent somatotroph adenomas have morphologic features similar to those of sparsely granulated somatotroph adenomas. Silent lactotroph adenomas and silent thyrotroph adenomas exhibit morphologic features corresponding to those of their functioning counterparts. Silent corticotroph adenomas are usually associated with hyperprolactinemia even in cases without obvious stalk involvement. There are two morphologic variants. Type I silent corticotroph

adenomas correspond morphologically to the functioning densely granulated corticotroph adenoma. Type II silent corticotroph adenomas are similar to the sparsely granulated functioning corticotroph adenomas. The clinical inactivity of some corticotroph adenomas may be due to aberrant cleavage of the POMC molecule. Silent gonadotroph adenomas are morphologically identical to the functioning gonadotroph adenomas and represent the largest group of clinically nonfunctioning adenomas. Most tumors classified as null cell adenomas are silent gonadotroph adenomas composed of poorly differentiated cells with scattered foci exhibiting histologic features consistent with gonadotroph differentiation; these tumors generally exhibit SF-1 staining despite lack of detectable gonadotropin content. Oncocytomas represent silent gonadotroph adenomas with extensive oncocytic change (Figure 23). The tumor cells are usually arranged sheets or nests, and contain abundant granular eosinophilic cytoplasm, which corresponds ultrastructurally to mitochondrial accumulation in the cytoplasm. These tumors also generally exhibit SF-1 nuclear reactivity (3).

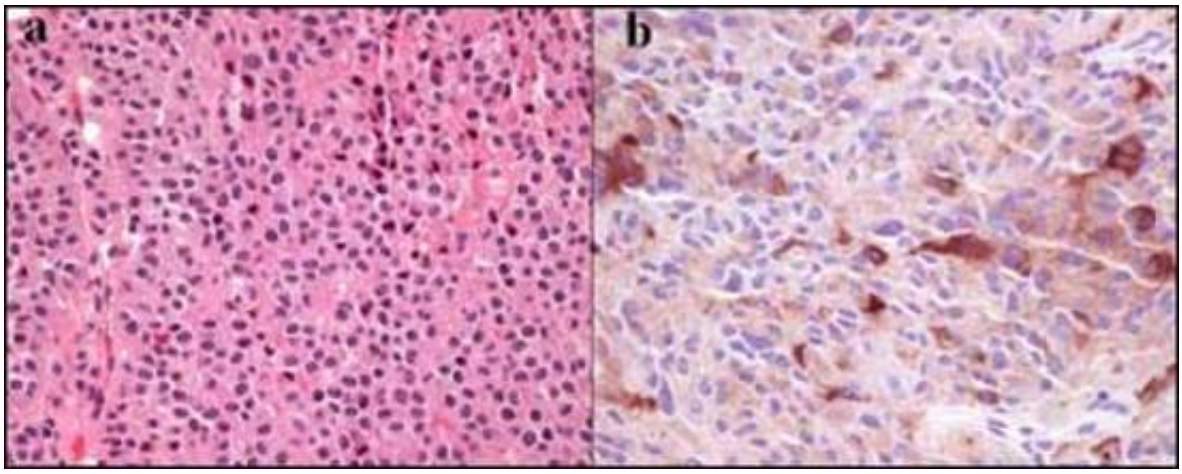

Figure 23. Oncocytomas represent silent gonadotroph adenomas with extensive oncocytic change. The tumor cells are arranged solid nests, and contain abundant granular eosinophilic cytoplasm (a). Immunohistochemistry identifies SF-1 nuclear reactivity and cytoplasmic staining for α-subunit as well as β-subunits of the gonadotropins, e.g. β-FSH in this tumor (b).

Despite advances in morphologic classification of adenohypophysial cells, due to improved tissue fixation, more specific and sensitive antibodies, and transcription factors that identify cell differentiation, there remain a minority of pituitary adenomas that defy definitive classification on based on histological, immunohistochemical, and ultrastructural examination. Poorly differentiated adenomas are negative for all hormones and transcription factors and exhibit no ultrastructural markers of the known adenohypophysial cell types (3).

The tumor identified as “female type gonadotroph adenoma” (149) is a tumor that is usually clinically silent, immunohistochemically plurihormonal, and characterized by a distinctive ultrastructural feature of dilated, saccular Golgi bodies known as “honeycomb Golgi”. The cytogenesis of this lesion is not known, but recent data suggest that the honeycomb Golgi is not

a specific finding and some of these tumors may actually represent corticotroph adenomas (149a).

PLURIHORMONAL PITUITARY ADENOMAS

Occasionally, pituitary adenomas elaborate multiple hormones. Most often, this is due to known regulatory factors; rarely, products of different hormone families are produced. These adenomas may be fully functioning, partially functioning (in which only one component is clinically apparent), or silent. The most common combination is excessive production of GH and PRL, or GH, PRL and TSH, resulting in acromegaly/gigantism accompanied by hyperprolactinemia and even hyperthyroidism. This pattern of plurihormonality is accounted for by the expression of Pit-1 that regulates the expression of these various hormones by related cells. Other combinations of unrelated hormones have been reported (3). The interpretation of the individual combinations must be evaluated with caution, and may in some cases be artefacts of antibody cross-reactivity.

Monomorphous plurihormonal adenomas are composed of one cell type that can produce multiple hormones; this is supported by cytoplasmic immunoreactivity for two or more hormones within the same cell. Plurimorphous plurihormonal adenomas are composed of at least two cell types, each of which exhibits a characteristic immunohistochemical and ultrastructural profile. These may represent “collision” tumors (150;151). Silent subtype III adenomas are rare and aggressive plurihormonal tumors that are identified by unique ultrastructural features (152). The large tumor cells have nuclei that are located at one pole and may contain spheridia. There is abundant well-developed rough endoplasmic reticulum with prominent, tortuous Golgi complexes, and abundant groups of mitochondria. Small secretory granules are localized to attenuated, interdigitating cell processes. This lesion is considered more aggressive and local recurrence is not uncommon; there may be a role for radiotherapy for this relatively radiosensitive lesion.

PITUITARY CARCINOMA

Malignant tumors of adenohypophysial origin are defined by the ability to metastasize (3;153). Although many pituitary adenomas are widely invasive, destructive of adjacent tissues, and lethal, they are not classified as malignancies. The pathogenesis of the very rare pituitary carcinoma is not known. H-ras point mutations have been reported in some metastatic foci, but not in the corresponding primary tumor (154;155). Immunoreactivity for p53 has been reported, but p53 mutations are not found in these lesions and there is insufficient evidence at this point to draw any conclusions regarding the mechanism of the apparent accumulation of p53 protein (156).

Pituitary carcinomas generally present initially as pituitary adenoma. They can be associated with any form of hormone excess (157-162), or they may be clinically nonfunctioning lesions (163;164). Only the subsequent development of metastases identified the lesion as malignant. The most common sites of metastasis include the subarachnoid space, brain parenchyma (not including areas of direct invasion), cervical lymph nodes, bone, liver, and lungs. Examination of

the primary tumor usually reveals non-specific morphologic features such as hypercellularity, hemorrhage, necrosis, mitoses, nuclear pleomorphism, and invasion; none of these features either individually, or in combination, are reliable indicators of malignancy. Immunohistochemistry and electron microscopy are used mainly to characterize the tumor based on the classification scheme applied to the more common adenomas (165).

OTHER PRIMARY TUMORS OF THE SELLAR REGION

CRANIOPHARYNGIOMA

This benign but locally invasive tumor, which originates from the remnants of Rathke's pouch, represents 2 to 4 percent of all intracranial neoplasms (166). It is the most common sellar tumor in children and accounts for 10% of all childhood CNS tumors. Craniopharyngiomas can occur at all ages but the peak incidence occurs from 5 to 20 years old with a second smaller peak occurring in the sixth decade. Some series show a male predominance.

Three quarters of patients have mass effects with headaches and visual field disturbances (50). Patients may have psychiatric disturbances, nausea, vomiting, and somnolence. Hypopituitarism is identified in the majority but is not often the presenting complaint. In contrast to patients with large pituitary adenomas, hyperprolactinemia is found in less than half of patients (167;168) and about 25% of patients have diabetes insipidus. Children may present with dwarfism.

Radiologic evaluation reveals a variably cystic lesion; only 10% are entirely solid with no cystic component. An enlarged or eroded sella turcica is encountered in 50% of cases; suprasellar calcification is present in more than 50% of cases. MRI is the preferred technique to determine the extent of the lesion but unlike CT does not show the calcification; there is often a strong T1 signal on MRI in the absence of contrast due to high lipid content.

The natural history of these lesions is extensive infiltration with significant tissue damage. Infiltration may involve the hypothalamus or extend to as high as the third ventricle. Complete surgical resection is curative (169). However, the highly infiltrative nature of this lesion often results in incomplete resection with a subsequent high recurrence rate of 10 to 62%; this is especially true in younger patients. Post-operative radiation has been advocated to reduce recurrence. Hormone replacement may be necessary for persistent hypopituitarism.

Complications of untreated disease include hydrocephalus if there is extension and obstruction of the third ventricle, and rupture with abscess formation. A single case of malignant transformation in a craniopharyngioma has been reported (170).

Craniopharyngiomas are entirely suprasellar in 85% of cases; an intrasellar component is present in only 15%. Most of these tumors are larger than 1 cm at the time of diagnosis. They are well circumscribed but not necessarily encapsulated and usually contain a thick oil-like fluid resembling "black sludge". The cyst fluid has been shown to contain HCG (170a). Other features recognized grossly include the presence of cholesterol and calcification.

By light microscopy, the tumor is characterized by islands of epithelial cells and cysts within a loose fibrous stroma (Figure 24). Cholesterol clefts are common. There is often keratin debris, which forms the nidus for calcification. Occasionally, there is a mixed chronic inflammatory infiltrate composed of lymphocytes, plasma cells and macrophages. Although grossly well delineated, microscopically these tumors frequently have infiltrative borders with associated gliosis of the adjacent brain. Two histologic types are identified. The adamantinomatous variant has a prominent stellate component and resembles the dental ameloblastic organ and other adamantinomas. The less common papillary variant is found in adults. This tumor is characterized by pseudopapillary squamous epithelium in a solid or cystic pattern; palisading, fibrosis, and cholesterol accumulation are usually absent. This variant has a somewhat better prognosis than the adamantinomatous variant. By immunohistochemistry, the presence of cytokeratin reactivity confirms the epithelial nature of these tumors. Immunoreactive HCG□ can be demonstrated in some of the cells (171a). Ultrastructural examination reveals tonofilaments, intercellular junctions, and the absence of secretory granules.

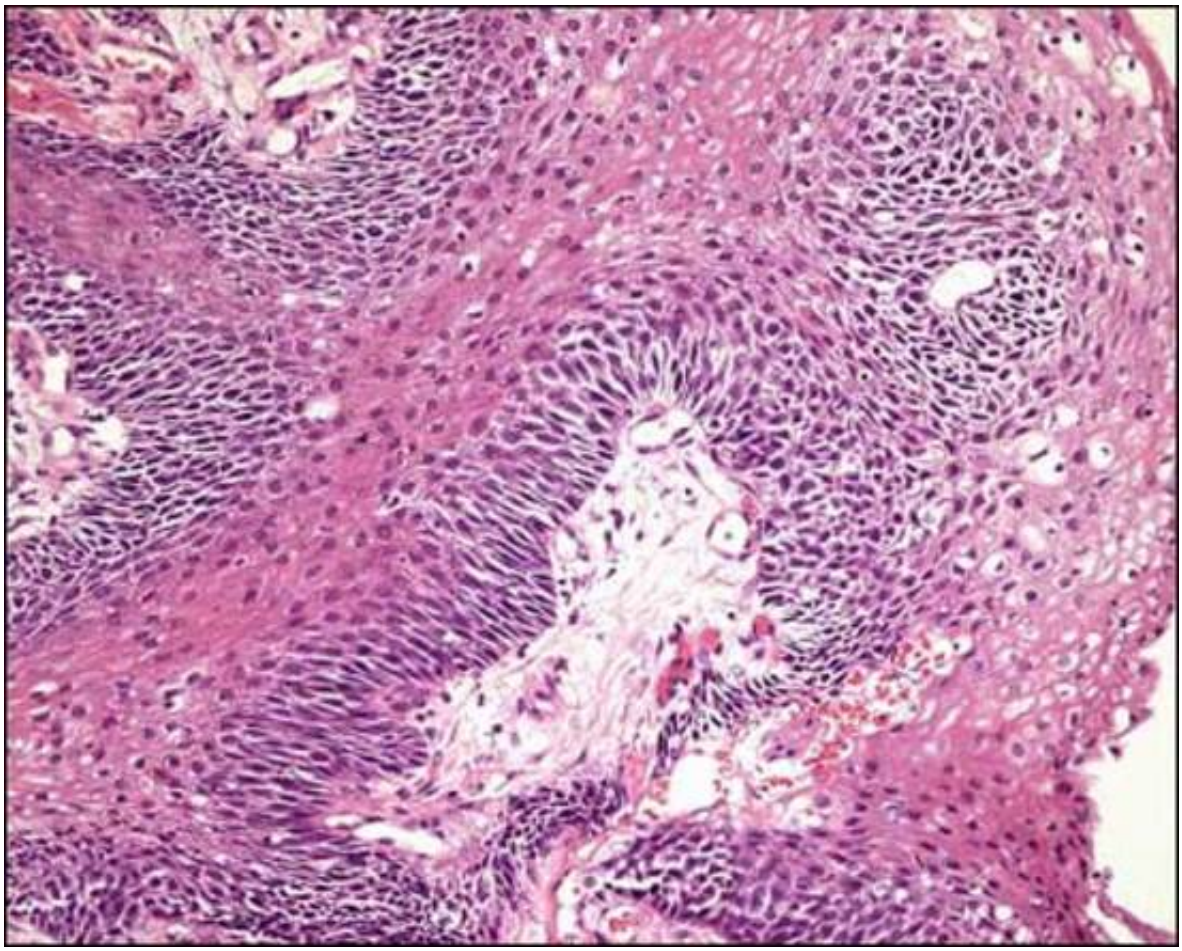

Figure 24. Craniopharyngioma is characterized by islands of epithelial cells with a loose fibrous stroma.

Beta-catenin gene mutations have been documented in adamantinomatous but not papillary craniopharyngiomas (171b), suggesting a role for □-catenin in tumorigenesis. Cytoplasmic and nuclear localization of immunohistochemical reactivity for □-catenin correlates with mutation; in contrast papillary craniopharyngiomas with no mutations show exclusively membranous expression of this protein (171b). There is evidence that stromal cells may also harbor □-catenin mutations, suggesting that the stroma may be a true neoplastic component rather than reaction to the proliferating epithelium (171b).

NEURONAL TUMORS

These tumors are also known as “gangliocytomas” or “ganglioneuromas” (3). They are composed of mature neurons, most likely derived from the ganglion cells of the hypothalamus. Clinically, they can present with mass effects, hypothalamic dysregulation, hypopituitarism, and hyperprolactinemia (171). Because these tumors have the ability to synthesize hypothalamic peptides, they may sometimes be associated with other hormonal syndromes including acromegaly, precocious puberty, or Cushing’s disease (171). Histologically, they are composed of mature ganglion cells with abundant cytoplasm that contains Nissl substance, and large nuclei with prominent nucleoli (Figure 25). Binucleate or even multinucleated cells are not uncommon. The tumor cells are distributed within a variable stroma composed of neuroglia, or fibrous tissue with small vessel proliferation. These tumors are immunoreactive for synaptophysin and neurofilaments and may contain hypothalamic peptides. Ultrastructurally, the tumor cells resemble mature neurons with abundant endoplasmic reticulum, mitochondria, and neurofilaments. Secretory granules are concentrated in neuronal processes. The neuronal lesions associated with acromegaly have often been composite tumors with a pituitary adenoma component, usually a sparsely granulated somatotroph adenoma.

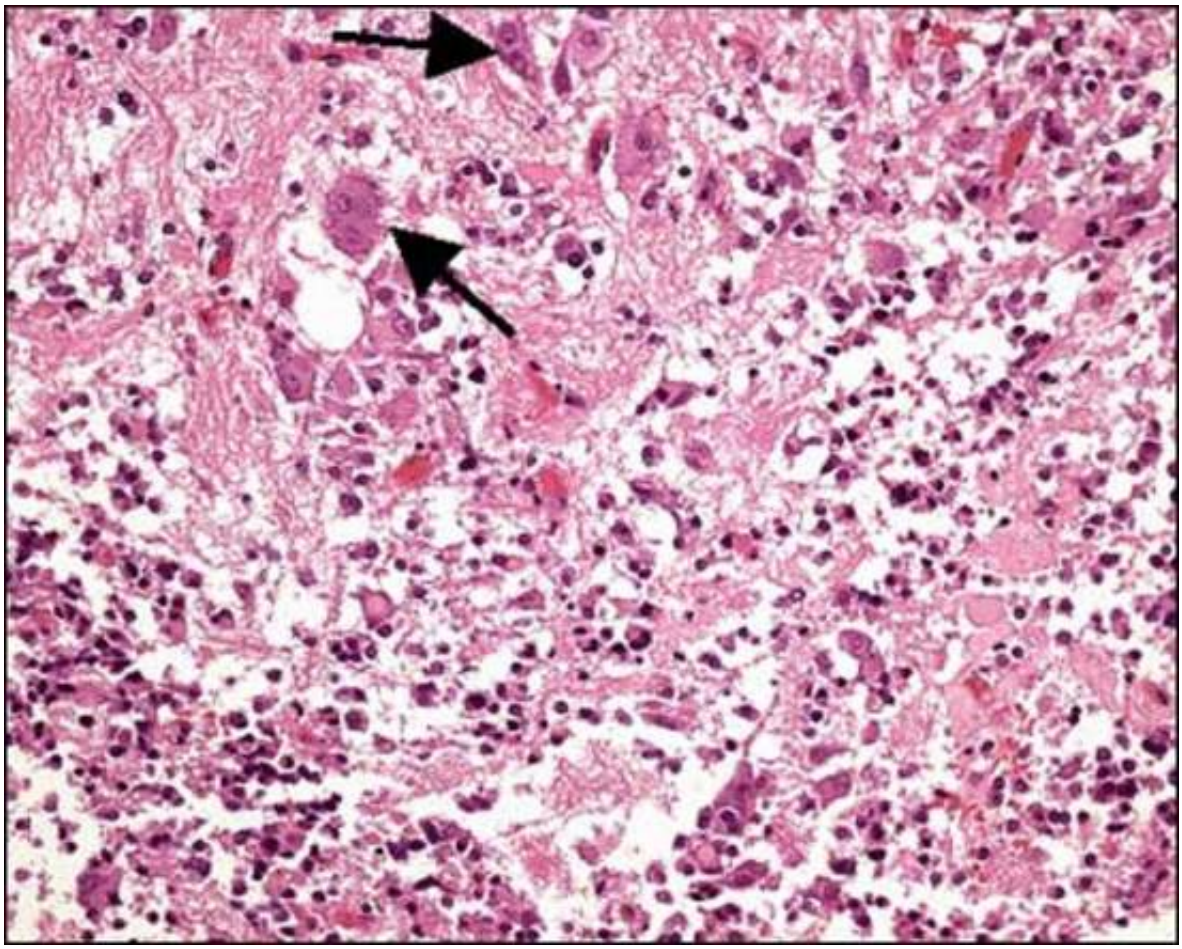

Figure 25. Hypothalamic gangliocytomas are composed of mature neurons that may be binucleate (arrows). This tumor is associated with a sparsely granulated somatotroph adenoma (bottom) and the neurons contained immunoreactivity for GRH.

GLIOMAS

These are neoplasms of neuroglia and include astrocytomas, oligodendrogliomas, and ependymomas (3). The pilocytic astrocytoma, which is most common young patients, is the most common glial tumor of the sellar region (172). These lesions can be sporadic, associated with inherited conditions, or may follow cranial irradiation (173;174). Low-grade gliomas occurring in children have a good prognosis. Post irradiation gliomas and those affecting the optic nerve are aggressive and rapidly lethal.

MENINGIOMAS

Meningiomas are neoplasms of the meninges, most commonly of arachnoid origin. They occur more frequently in females. Meningiomas of the sellar region account for up to 20% of all meningiomas. They can present with neurological deficits, visual field defects, hypopituitarism,

and hyperprolactinemia due to stalk compression (175). Completely intrasellar meningiomas are rare (176). They have been reported following radiotherapy for pituitary adenoma (177-179).

GRANULAR CELL TUMORS

Granular cell tumors are benign neoplasms of uncertain histogenesis found in the neurohypophysis or distal pituitary stalk (180;181). Most of these tumors are small and are incidental autopsy findings. Occasionally, they present with visual field deficits. Diabetes insipidus is rare. These tumors are unencapsulated and composed of cells with abundant, granular, eosinophilic cytoplasm. The granules are PAS positive and diastase resistant. The tumor cells exhibit variable immunoreactivity for the histiocytic markers alpha-1-antitrypsin, alpha-1-antichymotrypsin, and cathepsin B. They are usually nonimmunoreactive for GFAP and S-100 protein (182). Ultrastructurally, the granular cells have phagolysosomes containing debris and electron dense material.

CHORDOMAS

Chordomas are rare midline tumors derived from notochord remnants (183). They usually occur in patients over thirty years old. These tumors are slow growing but locally aggressive. Clinically, patients with parasellar chordomas can present with hypopituitarism. Radiologically, they are lobulated, osteolytic lesions with foci of calcification. Elevation of the periosteum is a characteristic feature of chordomas. The treatment of choice is surgical excision. Tumors that are incompletely resected can be irradiated. Mean survival from time of diagnosis is approximately 5 years. Grossly, chordomas are gelatinous, lobulated, and calcified. Microscopically, the tumors are composed of large polygonal cells called “physaliphorous” cells because of their bubbly cytoplasmic vacuoles containing glycogen and neutral mucins. The cells are arranged in solid sheets or trabeculae within a stroma of acidic mucin. The tumor cells are immunoreactive for low molecular weight cytokeratins, epithelial membrane antigen (EMA), S100 protein, and sometimes carcinoembryonic antigen (CEA). Ultrastructurally, desmosomes and microvilli are present. The rough endoplasmic reticulum forms concentric rings around mitochondria.

SCHWANNOMAS

These tumors are also known as neurolemmoma. Schwannomas of this region are derived from the Schwann cells surrounding cranial nerves. They are rare tumors that can present as a sellar mass with or without hypopituitarism or hyperprolactinemia (184-186). These tumors are usually benign. Surgical resection is the treatment of choice. Histologically, these tumors are usually encapsulated lesions composed of spindle-shaped cells arranged into the classic Antoni A and Antoni B areas. Verocay bodies result from palisading of tumor cells in Antoni A areas. The tumor cells are immunoreactive for S-100 protein. Ultrastructural examination reveals basal lamina and pathognomonic long-spacing collagen.

GERM CELL TUMORS

These are midline tumors that arise from residual germ cells. They include germinomas, embryonal carcinomas, teratomas, endodermal sinus tumors, and choriocarcinomas. These tumors represent less than 1% of intracranial tumors in adults (187). However, in children, germ cell tumors account for approximately 6.5% of all intracranial neoplasms (188). They are relatively rare after age twenty, with males more frequently affected than females. The most common site of intracranial involvement is the pineal gland, followed by the suprasellar region (189). Within the sellar region, pure germinomas and pure teratomas are the predominant subtypes. Mixed germ cell tumors are also common; they usually contain a germinoma in combination with some other component (190;191). Tumors that produce beta-hCG may result in precocious puberty.

HEMATOLOGIC TUMORS

Neoplastic proliferations of myeloid, lymphoid or plasmacytoid cells within the hypophysis and hypothalamus usually occur as part of a systemic disorder. However, very rarely, the hypophysis and/or hypothalamus may be the primary site of involvement (192-194). Histologically, these neoplasms are similar to their extracranial counterparts. They are most commonly non-Hodgkin's lymphomas composed of B-cells (195).

LANGERHANS' CELL HISTIOCYTOSIS

Langerhans' cell histiocytosis is characterized by proliferation of the Langerhans' cell, which is a special type of histiocyte with dendritic processes and antigen presenting capabilities. This disease can be unifocal, multifocal, or disseminated, and is separated into three clinicopathologic entities: Letterer-Siwe disease, eosinophilic granuloma, and Hand-Schuller-Christian disease (3). Characteristically, the granulomas may produce cranial diabetes insipidus with or without growth hormone and gonadotrophin and occasionally other hormone deficiencies due to anterior hypothalamic infiltration although there may also be infiltration of the pituitary stalk itself.

These lesions are characterized by large Langerhans' cells that have abundant pink cytoplasm with characteristic indented or "kidney-bean" shaped nuclei. They are usually accompanied by a mixed inflammatory infiltrate including lymphocytes, plasma cells, and eosinophils. The Langerhans' cells are immunoreactive for CD1a and S-100 protein. Ultrastructurally, the presence of Birbeck granules within the cytoplasm is diagnostic (195;196).

MESENCHYMAL TUMORS

Tumors arising from mesenchyme can be derived from vessels, fat, bone, cartilage, or fibrous tissue. They can be benign or malignant. Involvement of the sellar turcica by such neoplasms is uncommon; they usually manifest with mass effects and variable hypofunction of anterior or posterior pituitary function. Those reported in the sellar region include hemangioma (197;198), glomangioma (199), hemangioblastoma (200), lipoma (3), enchondroma (201), chondroma (202;203), chondrosarcoma (204), chondromyxoid fibroma (205), giant cell tumor (206), alveolar soft part sarcoma (207), osteosarcoma (208), and fibrosarcoma (209). They can be sporadic, or

can occur as part of a clinical syndrome such as von Hippel Lindau disease (200). However, most commonly, sarcomas of the sellar region develop as a result of previous irradiation for lesions such as pituitary adenoma or craniopharyngioma (210).

METASTATIC TUMORS TO THE HYPOPHYSIS AND SELLA TURCICA

The pituitary gland, being a highly vascular organ, can be the target of blood-borne metastases from many malignancies. Metastatic tumors to the pituitary gland are not an uncommon event; the frequency has been reported to be as high as 27 percent. Involvement of the neurohypophysis is more common than the adenohypophysis. The most common sites of origin are lung, breast, and gastrointestinal tract (211-214).

Metastatic tumors to the pituitary gland are usually not among the most prominent clinical complaints of patients with disseminated malignancy and are usually discovered at autopsy. They may occasionally present as a sellar tumor in a patient with an occult primary. Clinically they are distinguished from primary pituitary adenomas by the prominence of diabetes insipidus, and mass effects such as headaches, visual field defects, ptosis, and ophthalmoplegia; hypopituitarism is less evident and occurs when adenohypophysial involvement is extensive. In rare cases, metastatic involvement of a pituitary adenoma may result in rapid increase in tumor size and/or sudden worsening symptoms (215-218).

MISCELLANEOUS LESIONS

Other rare and unusual lesions of the pituitary region include inflammatory pseudotumors (219), aneurysm (220), meningoencephlocele (221), hamartomas and choristomas (222;223), and brown tumor of bone (126).

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