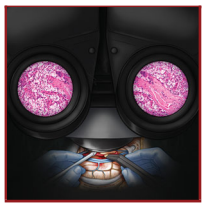
Neuropathology of Pituitary Adenomas and Sellar Lesions



Peter J. Kobalka, MD*
Kristin Huntoon, PhD, DO‡
Aline P. Becker, MD, PhD§

*Department of Pathology and Laboratory Medicine, The Ohio State University Medical Center, Columbus, Ohio; ‡Department of Neurosurgery, The Ohio State University Medical Center, Columbus, Ohio; §Department of Radiation Oncology, The Ohio State University Medical Center, Columbus, Ohio

Correspondence:
Peter J. Kobalka, MD,
Department of Pathology and Laboratory Medicine, D590,
The Ohio State University Medical Center,
460 W 10th Ave,
Columbus, OH 43210, USA.
Email: Peter.Kobalka@osumc.edu

Received, May 21, 2020.
Accepted, October 22, 2020.
Published Online, January 20, 2021.

The pituitary gland is the site of numerous neoplastic and inflammatory processes. The overwhelmingly most frequent tumors arise from cells of the anterior lobe, the pituitary neuroendocrine tumors (PitNETs). Immunohistochemistry assay staining for pituitary hormones is the core tool for classifying PitNETs, resulting in the diagnosis of somatotroph PitNETs, lactotroph PitNETs, and so on. For cases showing no hormonal expression, the updated WHO classification system now considers the assessment of several transcription factors: PIT-1 (pituitary-specific POU-class homeodomain transcription factor); T-PIT (T-box family member TBX19); and SF-1 (steroidogenic factor regulating gonadotroph cell differentiation) before rendering a diagnosis of null cell adenoma. Other tumors and disease processes of this site often mimic PitNETs radiographically and sometimes even clinically (ie, compression of the optic chiasm). These potpourri of processes include germ cell neoplasms (especially germinomas), tumors that originate from Rathke's pouch (craniopharyngiomas, Rathke's cleft cyst), tumors that originate from the posterior lobe of the pituitary (pituicytoma, spindle cell oncocytoma, granular cell tumor), and tumors that originate from the meninges (especially meningiomas). In addition to neoplasms, several described inflammatory and related conditions exist that need to be distinguished from PitNETs. These include lymphocytic hypophysitis and Langerhans cell histiocytosis, a neoplastic disorder of histiocytes. In this review, we aim to briefly describe the main pituitary and sellar lesions, with emphasis on the most common tumors, the PitNETs.

KEY WORDS: Pituitary adenoma, Craniopharyngioma, Sellar, Neurohypophysitis, Germ cell, Inflammatory, Neuropathology

Neurosurgery 88:900–918, 2021 DOI:10.1093/neuros/nyaa548 www.neurosurgery-online.com

Embryologically, the pituitary gland has 3 lobes: the anterior and intermediate lobes form the adenohypophysis (stomodeal ectoderm), and the posterior lobe to the neurohypophysis (neuroectoderm) (Figure 1A-1E). The adenohypophysis has lobulated collections (acini) of neuroendocrine cells, which secrete pituitary hormones (Figure 1B). The intermediate lobe consists of watery, proteinaceous cyst-like structures. The posterior lobe has pituicytes (specialized support astrocytes) and Herring bodies. The hypophyseal portal system allows transport of hormones from the hypothalamus to the anterior pituitary.[1]

Because of this heterogeneous histological constitution, the pituitary and the sellar region may originate numerous benign and malignant neoplasms and non-neoplastic diseases. This review will address lesions that neurosurgeons typically already know require aggressive treatment (eg, craniopharyngioma and adrenocorticotropic hormone (ACTH)-producing lesions, ie, Cushing disease) as well as newer entities, including pituitary blastoma and rarer aggressive lesions, such as plurihormonal adenomas and pituitary carcinoma.

ABBREVIATIONS: ACTH, adrenocorticotropic hormone; **βHCG,** beta human chorionic gonadotrophin; **EGB,** eosinophilic granular body; **ESS,** empty sella syndrome; **FSH,** follicle-stimulating hormone; **GFAP,** glial Fibrillary acidic protein; **GH,** growth hormone; **H&E,** hematoxylin and eosin staining; **IHC,** immunohistochemistry; **LH,** luteinizing hormone; **MEN1,** multiple endocrine neoplasm 1; **PAS,** periodic-acid-Schiff; **PitNET,** pituitary neuroendocrine tumors; **TSH,** thyroid stimulating hormone; **TTF-1,** thyroid-transcription factor 1

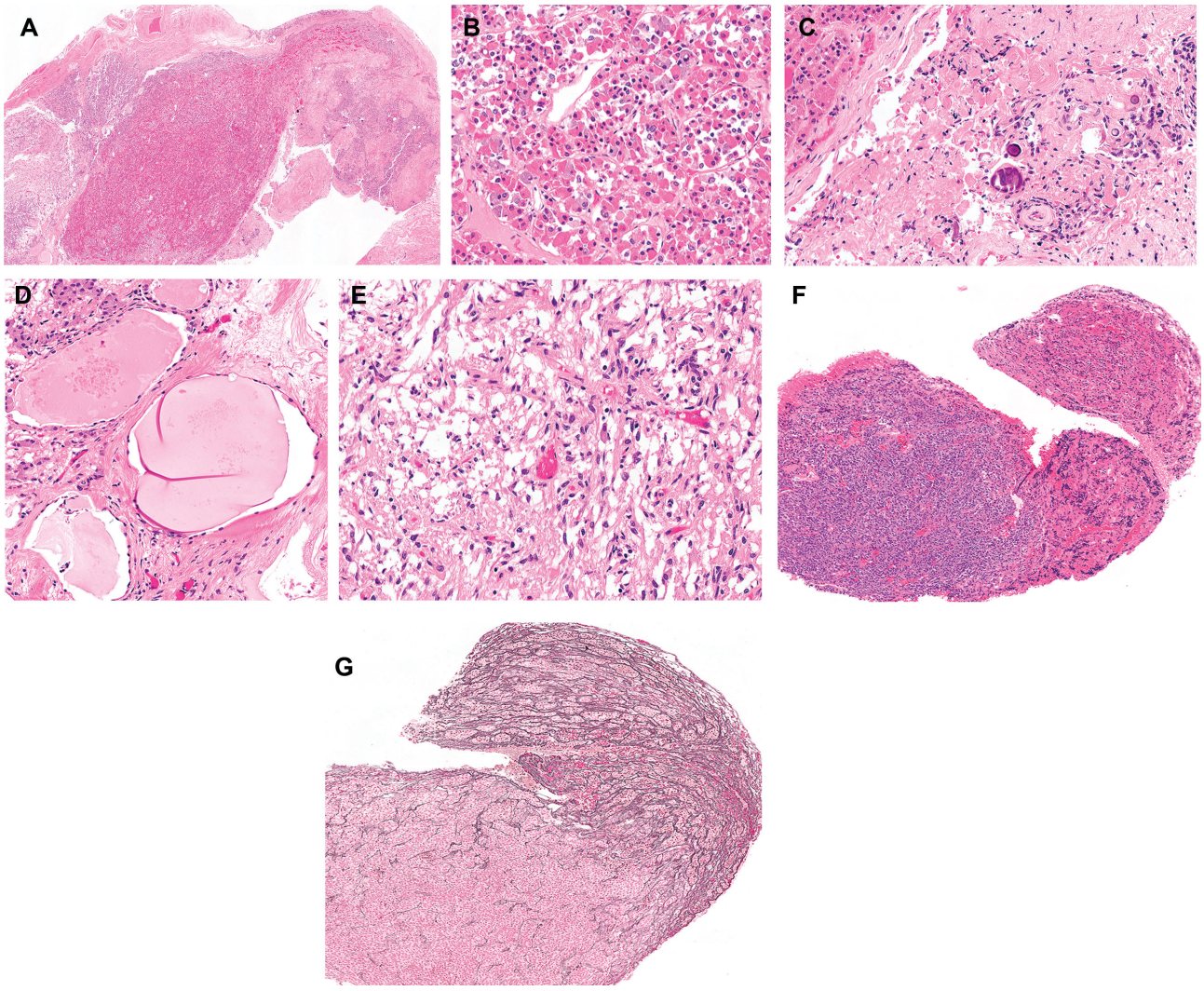


FIGURE 1. *Normal pituitary microanatomy and pituitary adenoma. Normal pituitary:* **A**, *the anterior lobe (adenohypophysis—AL), the source of pituitary adenomas; the intermediate lobe (IL), the source of Rathke cleft cyst; the posterior lobe (neurohypophysis—PL), the source of pituicytomas, etc; the meninges (M) partially covering the gland that can give rise to meningeal-based neoplasms in this location (especially meningiomas); and the rich capillary network (CN) of the hypothalamic-hypophyseal portal system, with scattered, intervening benign pituitary acini (H&E, 20×).* **B**, *Normal adenohypophysis consisting of clusters of acini composed of basophilis, eosinophils, and chromophobes (H&E, 200×).* **C**, *Meninges showing benign meningothelial cells and psammoma bodies (arrows). These are the source of meningiomas (H&E 100×).* **D**, *Intermediate lobe, composed of protein-filled cystic structures (H&E 40×).* **E**, *Normal posterior pituitary. The spindled cells (pituicytes) tend to aggregate around vessels (H&E 200×). Pituitary adenoma:* **F**, *H&E-stained sections show pituitary adenoma (PA) and normal pituitary (NP). The normal pituitary grows in small, well-formed lobular collections of cells (acini), whereas adenomas have distorted architecture, here growing in sheets (40×).* **G**, *Reticulin histochemical stain highlights the disrupted connective tissue framework within the adenoma (40×).*

TUMORS OF THE ADENOHYPOPHYSIS

The current 2017 WHO classification preserves the classification of pituitary adenomas and pituitary carcinomas.[2] For didactic reasons, the terms adenoma/carcinoma will be kept in this review, but the proposed changes in the nomenclature for pituitary neuroendocrine neoplasms (PitNETs)[3,4] are discussed.

Pituitary Adenomas

Pituitary adenomas, the most common neoplasms of this gland, are neuroendocrine neoplasms.[5] Pituitary adenomas are incidental findings in up to 20% of autopsies.[6] The majority of adenomas are situated in the sella turcica, although occasionally originate within the sphenoidal sinus (ectopic pituitary adenomas).[7] Normal anterior pituitary is arranged as

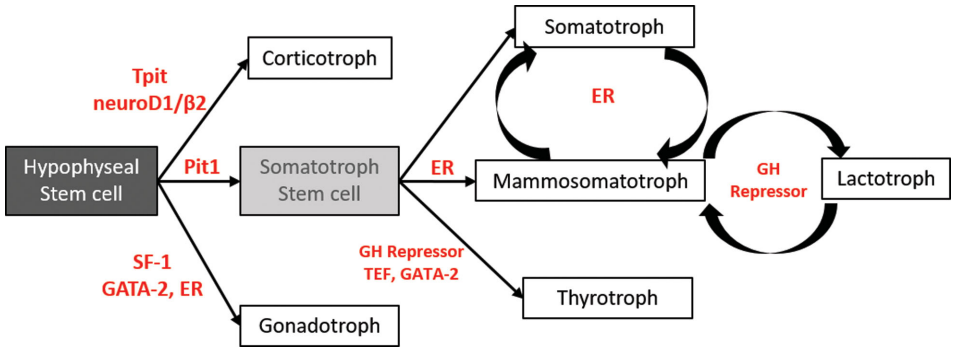


FIGURE 2. *The main transcription factors involved in anterior pituitary cell differentiation.*

TABLE 1. WHO Classification of Pituitary Adenoma (2017)

Adenoma type	Morphological variants	Pituitary hormones and other immunomarkers	Transcription factors and other co-Factors
Somatotroph adenomas	Densely granulated adenoma[a]	GH ± PRL ± α-subunit	PIT-1
	Sparsely granulated adenoma	GH ± PRL ± [CK]	PIT-1
	Mammosomatotroph adenoma	GH ± PRL (in same cells) ± α-subunit	PIT-1, ERα
	Mixed somatotroph-lactotroph adenoma	GH ± PRL (in different cells) ± α-subunit	PIT-1, ERα
Lactotroph adenomas	Sparsely granulated adenoma[a]	PRL	PIT-1, ERα
	Densely granulated adenoma	PRL	PIT-1, ERα
	Acidophilic stem cell adenoma	PRL, GH (focal and variable)	PIT-1, ERα
Thyrotroph adenoma		β-TSH, α-subunit	PIT-1
Corticotroph adenomas	Densely granulated adenoma[a]	ACTH, [CK]	T-PIT
	Sparsely granulated adenoma	ACTH, [CK]	T-PIT
	Crooke's cell adenoma	ACTH, [CK]	T-PIT
Gonadotroph adenoma		B-FSH, β-LH, α-subunit (various combinations)	SF-1, GATA-2, ERα
Null cell adenoma		None	None
Plurihormonal adenomas	Plurihormonal PIT-1 positive adenoma (previously called silent subtype 3 adenoma)	GH, PRL, β-TSH ± α-subunit	PIT-1
	Adenomas with unusual immunohistochemical combinations	Various combinations: ACTH/GH, ACTH/PRL	N/A

[a]Most common morphological variant.

Reprinted by permission from Copyright Clearance Center: Springer Nature, *Acta Neuropathologica*, The 2017 World Health Organization classification of tumors of the pituitary gland: a summary, M Beatriz S. Lopes, Copyright 2017.

small, even lobules within an intact connective tissue matrix. In contrast, pituitary adenomas expand and disrupt this framework, resulting in nodules or sheets (Figure 1F and 1G). The cells of pituitary adenomas have discrete (epithelioid) cell borders, rounded, granular cytoplasm with round nuclei and inconspicuous nucleoli. Cytoplasm staining quality ranges from chromophobic (sparsely granular pale) to eosinophilic (pink) to basophilic (purple) with hematoxylin and eosin staining (H&E). Cells will stain with markers for neurosecretory granules (synaptophysin and chromogranin) and epithelial markers (cytokeratins).[5] Pleomorphism may be seen, wherein nuclear size and shape of adjacent tumor cells can significantly vary; however, this should not in itself be interpreted as a feature of more aggressive clinical behavior or malignancy.

Although most pituitary adenomas occur sporadically, familial inherited syndromes associated with these neoplasms include multiple endocrine neoplasm 1 (MEN1), familial acromegaly, McCune-Albright syndrome, and Carney complex. Interestingly, these genetic syndromes are closely related to particular adenoma subtypes.[8,9] For example, somatotroph-type adenomas

TABLE 2. Likelihood of Recurrence of Pituitary Neuroendocrine Tumors

Low probability for recurrence	High probability for recurrence	Malignant (metastatic) tumor
Pituitary adenoma	Adenomas with elevated proliferative activity	Pituitary carcinoma
	Special subtypes (variants) of adenomas: Sparsely granulated somatotroph adenoma Lactotroph adenoma in men Silent corticotroph adenoma Crooke cell adenoma Acidophil stem cell adenoma Plurihormonal PIT-1 positive adenoma	

Reprinted by permission from Copyright Clearance Center: Springer Nature, *Acta Neuropathologica*, The 2017 World Health Organization classification of tumors of the pituitary gland: a summary, M Beatriz S. Lopes, Copyright 2017.

in familial acromegaly and McCune-Albright syndrome; MEN1 is associated with prolactinomas somatotropinomas, corticotropinomas, and thyrotropinomas, whereas somatotropinomas and thyrotropinomas are seen in Carney complex.[8,9]

Historically, pituitary adenomas were classified according to cytoplasmic staining of the neoplastic cells as acidophilic, basophilic, or chromophobic based on differences in histology stains, including H&E; however, this classification is highly subjective.[8] These histology stains were completed supplanted, with classification of pituitary adenomas now focusing on immunohistochemistry staining for hormones and/or clinically elevated hormone serum levels.[2,5] Many adenomas, however, neither stain for these markers nor produce a clinical syndrome. As a result, many hitherto adenomas were classified as null cell adenomas. After the discovery of upstream transcription factors driving tumorigenesis, the updated WHO classification system now focuses on adenohypophyseal cell lineage of undifferentiated cells, assessed by the expression of several transcription factors: PIT-1 (pituitary-specific POU-class homeodomain transcription factor), which enables the differentiation of somatotrophs, lactotrophs, or thyrotrophs; T-PIT (T-box family member TBX19), which influences cells into corticotrophs differentiation; and SF-1 (steroidogenic factor regulating gonadotroph cell differentiation) that drives gonadotroph production (Figure 2 and Table 1).[5,10-12] These transcription factors identify the cell lineage regardless of the expression of the actual hormone. As an example of their importance, a clinically silent adenoma may be negative for ACTH staining, but T-PIT reveals its true identity as a corticotroph adenoma, which carries an increased risk of recurrence (Table 2).[5,13]

Tumor invasion is a clinically significant prognostic factor of pituitary adenomas, apart from hormone and transcription factor immunohistochemistry findings.[2] Another important factor to be reported is an elevated Ki-67 proliferation index, assessed by immunohistochemistry (IHC).[2] Ki-67 is a marker of active phases of the cell cycle and stains cells actively dividing[14] and correlates with more aggressive tumor behavior.[15,16]

Somatotroph Adenoma

Somatotroph adenomas occur at any age (mean 47 yr).[17] Somatotroph adenomas represent up to 15% of all adenomas.[5] However, somatotroph adenomas often concomitantly produce other hormones; mammosomatotroph tumors, producing both growth hormone (GH) and prolactin, are the most frequent tumors in young patients with acromegaly and in cases of childhood onset gigantism.[18] Older adults often phenotypically present with acromegaly, but not gigantism.[8,19,20] Infrequently somatotroph-type adenomas even produce thyroid stimulating hormone (TSH) and cause clinical symptoms akin to thyrotroph-type adenomas (ie, hyperthyroidism).[2,21]

Histopathologically, 2 variants are recognized: densely and sparsely granulated. Although prone to subjectivity, this distinction is clinically significant, whereas densely granulated adenomas often respond to somatostatin analog therapy**,** sparsely granulated adenomas are resistant.[17,18,22] Clinically, densely granulated somatotroph adenomas (Figure 3A-3C) are the most common cause of acromegaly in adults and consist of cells with intensely eosinophilic cytoplasm.[23] GH immunohistochemistry is diffusely positive, whereas cytokeratins reveal a characteristic perinuclear pattern of reactivity.[17,24] In contrast, sparsely granulated adenomas are weakly eosinophilic to chromophobic (Figure 3D-3F).[17] Tumor cells contain pale, intracytoplasmic rounded, cytokeratin inclusions and "fibrous bodies."[2,5,8,17] Further, sparsely granulated adenomas tend to be larger at diagnosis, have a worse prognosis, and rarely may coexist with other neuroepithelial tumors, such as gangliocytomas.[17,18,25,26]

Lactotroph Adenoma

Prolactinomas are the most frequently diagnosed pituitary adenoma.[5,17,27] A female predominance exists, and patients are generally young to middle-aged adults (~20-40 yr of age).[12] Clinically, females tend to present with endocrinologically active microadenomas, resulting in galactorrhea,[8] whereas males have hormonally silent macroadenomas[8,28]; males carry an increased risk of recurrence, regardless of histologic type (Table 2).[17]

The 3 histologic subtypes of adenoma are sparsely granulated, densely granulated, and acidophilic stem cell.[12,17] Sparsely granulated adenomas (most common type) appear chromophobic and display quite variable growth patterns.[12,29] Prolactin immunohistochemistry is perinuclear and confined to the Golgi apparatus—unique to this histologic type (Figure 4A and 4B).[5,17] Rare cases have rounded calcium deposits or amyloid deposition (Figure 4C).[8,30,31] Densely granulated adenomas have eosinophilic to red (acidophilic) cytoplasm and

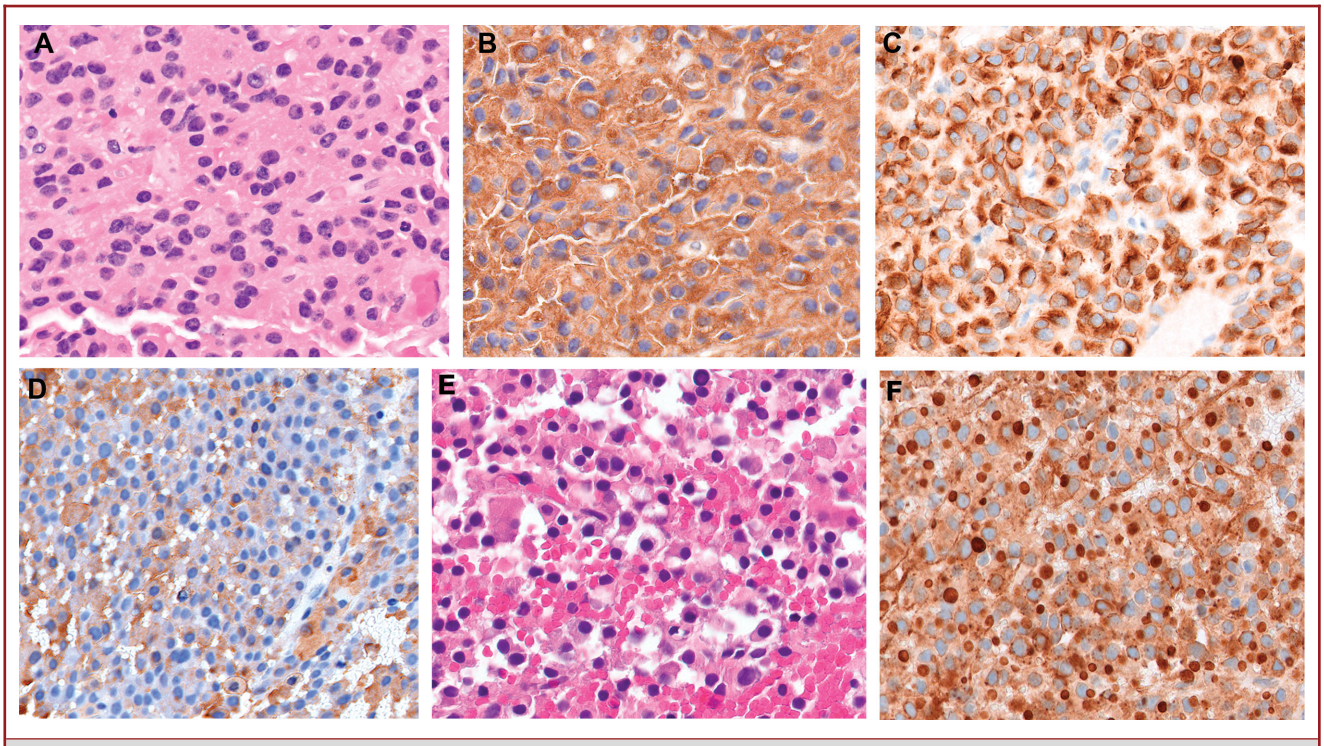


FIGURE 3. *Somatotroph pituitary adenomas.* **A-C**, *Densely granulated pituitary adenoma. Note the intensely eosinophilic tumor cells.* **B**, *Immunohistochemistry for GH is strong and diffuse;* **C**, *perinuclear staining for cytokeratin (CAM5.2).* **D-F**, *Sparsely granulated pituitary adenoma. Note the chromophobic to weakly eosinophilic sheets of cells.* **E**, *Immunohistochemistry for GH shows patchy expression,* **F**, *cytokeratin (CAM5.2) reveals an impressive number of intracytoplasmic "fibrous bodies," composed of keratin filaments. The diagnosis of mammosomatotroph adenoma and mixed somatotroph-lactotroph adenoma mainly rests on immunohistochemical distinction.*

cytoplasmic stain for prolactin (Figure 4C and 4D). These are rare but are considered an inherently aggressive type of adenoma in both sexes.[24,32] The third type is also the rarest variant, acidophilic stem cell adenomas. Their cells have brightly eosinophilic cytoplasm because of the accumulation of mitochondria (Figure 4E).[5,8] Immunohistochemistry may reveal positive staining for both prolactin and GH (Figure 4F).[8] As in some somatotroph adenomas, intracytoplasmic fibrous bodies may be seen with cytokeratin staining.[5,12] These tend to behave more aggressively, regardless of gender.[24,29,33]

The first-line treatment for lactotroph adenomas is dopamine agonists.[12] After pharmacological treatment, the tumor histopathology appears significantly different from the original tumor (Figure 4G and 4H). Surgery is considered secondary treatment, and is employed in cases that medical therapy has failed or not patient tolerated.[34,35]

Corticotroph Adenoma

Corticotroph type adenomas are fairly common (15% of adenomas) and are the most common adenoma in children (Figure 5).[29,36] Most are diagnosed in middle-aged females (~30-50 yr).[5,12] Patients have clinically recognizable symptoms of cortisol excess because of ACTH production (Cushing disease), although presenting with microadenomas.[12] In nearly 10% of cases, localization of a lesion is not possible,[9] either intraoperatively or with imaging studies.[37,38] Therefore, it is crucial for the surgeon to avoid intraoperative pathology consultation; this allows for multiple, additional, well-cut sections from the permanent specimens to help pinpoint the adenoma.[8,39]

The 3 recognized histologic subtypes of corticotroph adenomas are densely granulated, sparsely granulated, and Crooke cell adenoma.[12,17] Densely granulated adenomas are purple on H&E stains (basophilic) and are diffusely positive for ACTH immunohistochemistry (Figure 5A and 5B).[5,24,29] Sparsely granulated corticotroph adenomas are often inactive hormonally (silent adenomas), chromophobic to weakly basophilic, and show faint, if any, ACTH staining.[12] Crooke cell adenomas are a special subtype showing eosinophilic, cytoplasmic rings around the tumor cells that stain intensely with cytokeratins (Figure 5C and 5D).[8] Crooke cell adenomas, as well as silent corticotroph adenomas, tend to behave more aggressively (Table 2).[17,40,41]

Surgery is first-line therapy and without treatment; Cushing disease is fatal.[42] Care must be taken to exclude a

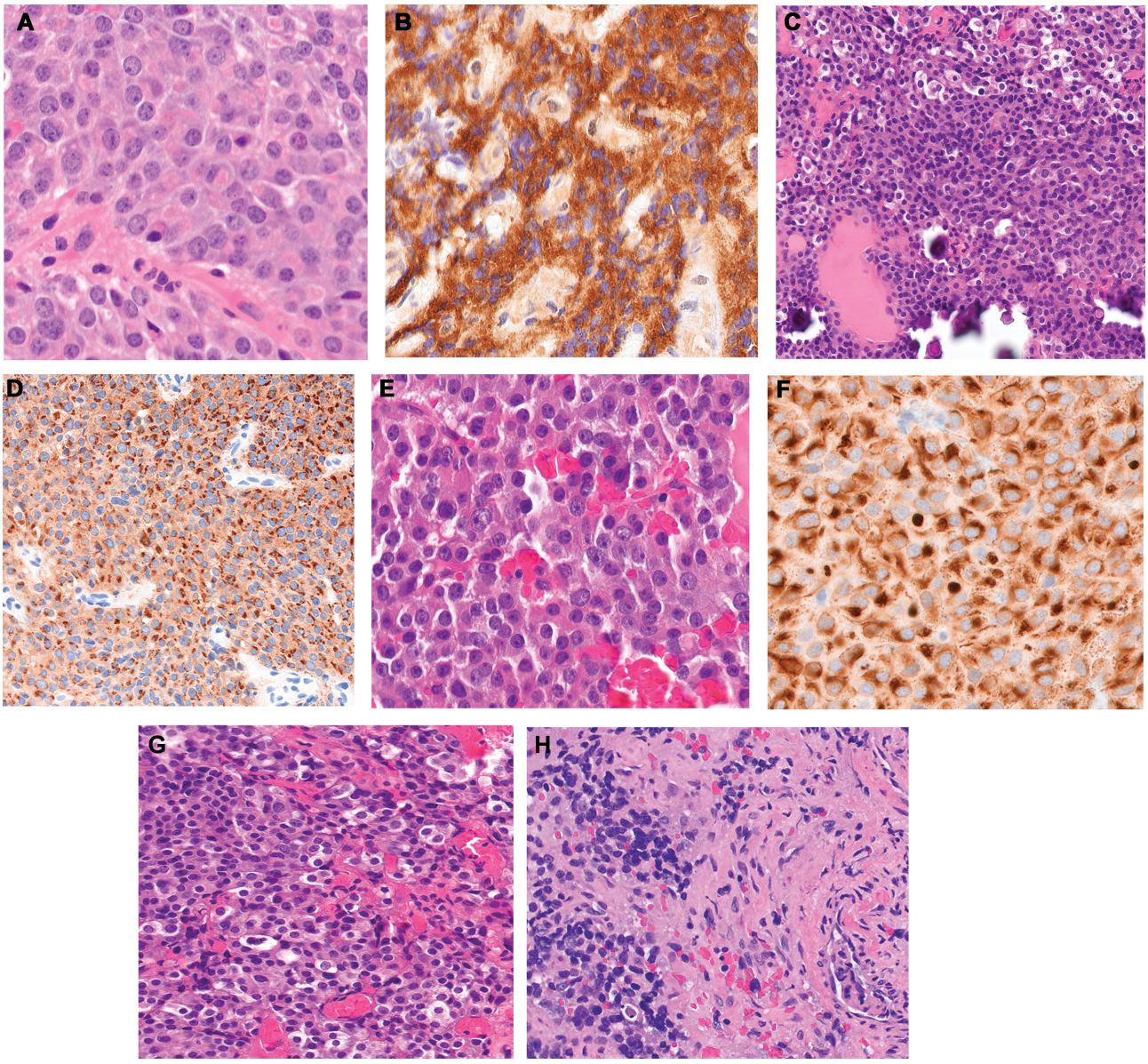


FIGURE 4. *Lactotroph pituitary adenomas.* **A** *and* **B**, *Lactotroph type pituitary adenoma densely granulated: cells are eosinophilic and stain diffusely with prolactin.* **C** *and* **D**, *Lactotroph type pituitary adenoma sparsely granulated: cells appear chromophobic, almost clear in appearance. Many circular calcifications are present, seen in some prolactinomas (arrows).* **D**, *Note the perinuclear reactivity for prolactin, unique to this subtype.* **E** *and* **F**, *Acidophil stem cell pituitary adenoma.* **E**, *Note the densely eosinophilic, almost red cytoplasm and vacuolization, due to accumulation of abnormally dilated mitochondria.* **F**, *Same case with cytokeratin staining, showing fibrous bodies.* **G** *and* **H**, *Pharmacologically treated lactotroph adenoma.* **G**, *Lactotroph adenoma before pharmacologic treatment and with treatment* ® **H**. *Treatment with dopamine agonists (like bromocriptine) induces fibrosis, with tumor cells losing their visible cytoplasm. The dense cell groups with very high nuclear cytoplasmic ratios can be confused for an embryonal tumor or a metastatic small cell carcinoma in the absence of a provided treatment history.*

nonpituitary cause of hypercortisolism (ie, ectopic secretion from a small cell neuroendocrine carcinoma of the lung, renal cell carcinoma, adrenal tumors, or glucocorticoid medications).[43] In cases in which a primary cause is erroneously attributed to an adrenal origin (and followed by bilateral adrenalectomy) rapid enlargement of the pituitary adenoma will result (Nelson syndrome) because of loss of end-organ feedback.[8,43] Adenomas in Nelson syndrome behave more aggressively and risk transforming into pituitary carcinomas.[43]

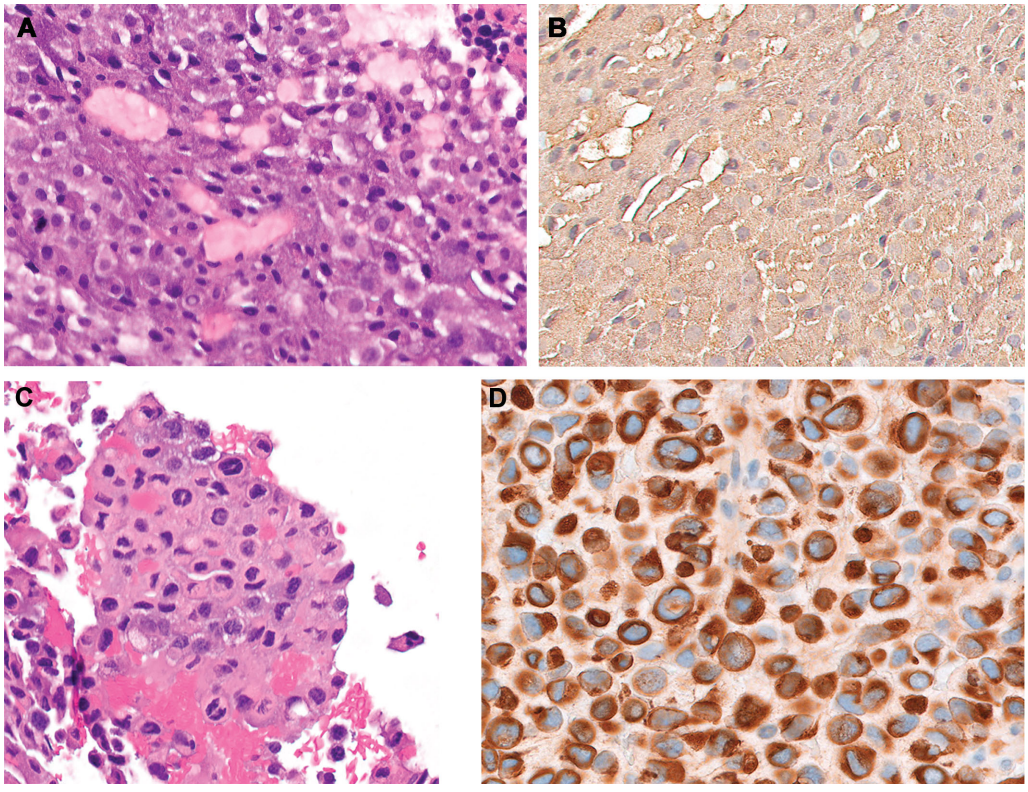


FIGURE 5. *Corticotroph type adenomas.* **A** *and* **B**, *Densely granulated pituitary adenoma.* **A**, *These adenomas are purple (basophilic) with H&E stains.* **B**, *ACTH is diffusely positive with immunohistochemistry.* **C** *and* **D**, *Crooke cell pituitary adenoma.* **C**, *Faint eosinophilic rings of filaments are seen on H&E.* **D**, *Crooke cell pituitary adenoma. These filaments stain intensely with cytokeratin by immunohistochemistry.*

Gonadotroph Adenoma

Gonadotroph adenomas generally present in adults (60-70 yr of age) and affect males more frequently.[8,17] In contrast to other hormonally defined adenoma subtypes, gonadotroph adenomas are usually clinically silent.[17] As a result, they typically present as macroadenomas with invasion of the cavernous sinus.[5,12] The risk of apoplexy is perhaps highest in this subtype.[8,44]

Histologically, tumor cells are chromophobic and arranged in perivascular pseudorosette-like formations, sheets, or sinusoidal patterns (Figure 6A). Immunohistochemistry for follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and the transcription factor SF-1 confirms their embryologic lineage and eliminates a null cell adenoma. Staining intensity generally varies between cases and is rarely diffuse (Figure 6B and 6C).[12] Treatment consists of surgery with complete resection, dramatically lowering the risk of recurrence.[8,45] Dopamine agonists or somatostatin therapy is generally ineffective.[8]

Thyrotroph Adenoma

Thyrotroph adenomas (~1% of adenomas) tend to occur in middle-aged females (sixth decade of life).[5,8] Often large, invasive tumors, they behave aggressively.[46,47] Clinically, hyperthyroidism is rarely associated via TSH secretion[5]; therefore, care must be taken to avoid performing thyroid ablation, as it may facilitate faster tumor growth.[12]

Microscopically, unlike other pituitary adenoma subtypes, the cells of this subtype are often spindly (Figure 7A and 7B), raising concerns for fibrous meningioma (Figure 7C and 7D), pituicytoma, or sellar schwannoma on frozen (Figure 7E and 7F).[8,12] Stromal fibrosis and calcifications are often seen.[12] Surgery with complete removal is generally effective.[12] Pharmacotherapy with somatostatin analogs is shown to decrease TSH levels in the majority of cases.[8,46,48]

Null Cell Pituitary Adenomas

By definition, null cell adenomas lack expression of pituitary hormonal markers and pituitary transcription factors. The majority are diagnosed as macroadenomas because of their nonfunctioning nature. Patients tend to be adults (mean age ~55 yr) with a slight male preference.[8,49]

Prior to the development of transcription factor, immunohistochemistry null cell adenomas were thought to correspond to 15%

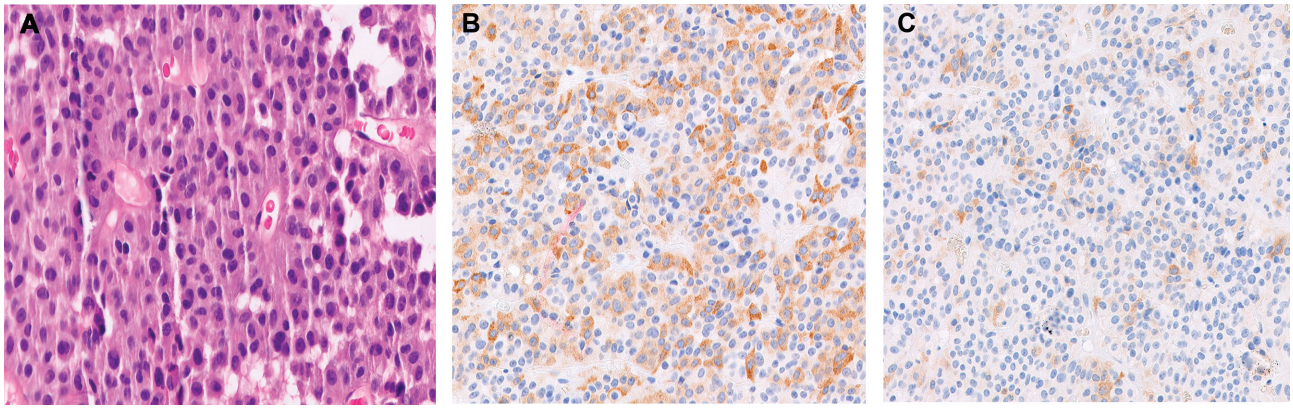


FIGURE 6. *Gonadotroph type adenomas.* **A**, *Note numerous perivascular pseudorosette-like formations composed of a central vessel lined by tumor cells. This adenoma may express both FSH* **B** *and LH* **C** *by immunohistochemistry.*

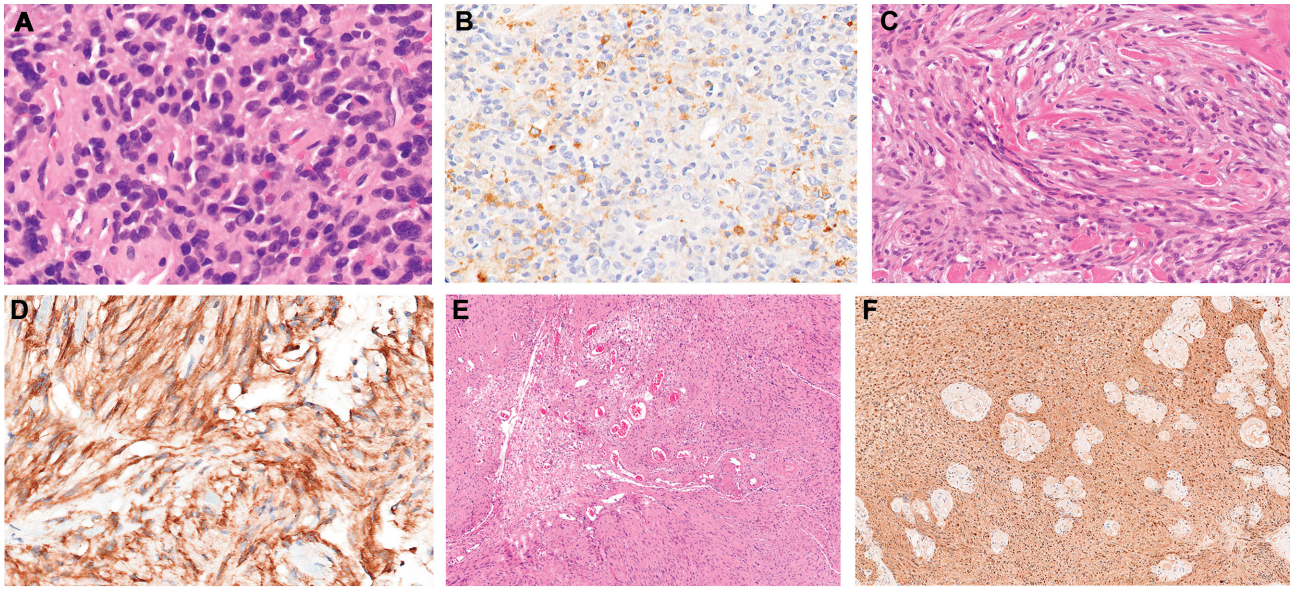


FIGURE 7. **A** *and* **B**, *Thyrotroph pituitary adenoma.* **A**, *H&E-stained sections often contain spindled tumor cells.* **B**, *TSH is usually patchy by IHC.* **C** *and* **D**, *Meningioma.* **C**, *Spindle cells are arranged in fascicles, often between collagen bundles.* **D**, *By immunohistochemistry, tumor cells stain with EMA. Pituitary hormones are negative.* **E** *and* **F**, *Schwannoma.* **E**, *A biphasic tumor composed of spindle cells in Antoni A (denser) and Antoni B (looser) areas, with scattered, Verocay bodies.* **F**, *By immunohistochemistry, S-100 is positive. Pituitary hormones are negative.*

of all pituitary adenomas diagnosed.[8,50] The true number now may only represent 1% of all pituitary adenomas, as transcription factor immunohistochemistry reveals most hitherto null cell adenomas being SF-1 positive, hormone negative gonadotroph adenomas.[51,52]

Histologically, the tumor cells are generally chromophobic and grow in sheets (Figure 8A) with no transcription factor expression (Figure 8B and 8C).[5,8,12] A diagnosis of exclusion, this can only be rendered after hormone and transcription factor stains are evaluated.[29,53] First-line treatment is surgical resection.[8,12] Incompletely excised tumors respond to radiation therapy.[12,54]

Plurihormonal and Double Adenomas

Plurihormonal adenomas, by definition, produce more than one hormone (Table 1). Included are single cell type adenomas producing multiple hormones, or adenomas composed of 2 distinct cell lineages (plurimorphous).[2] This group includes

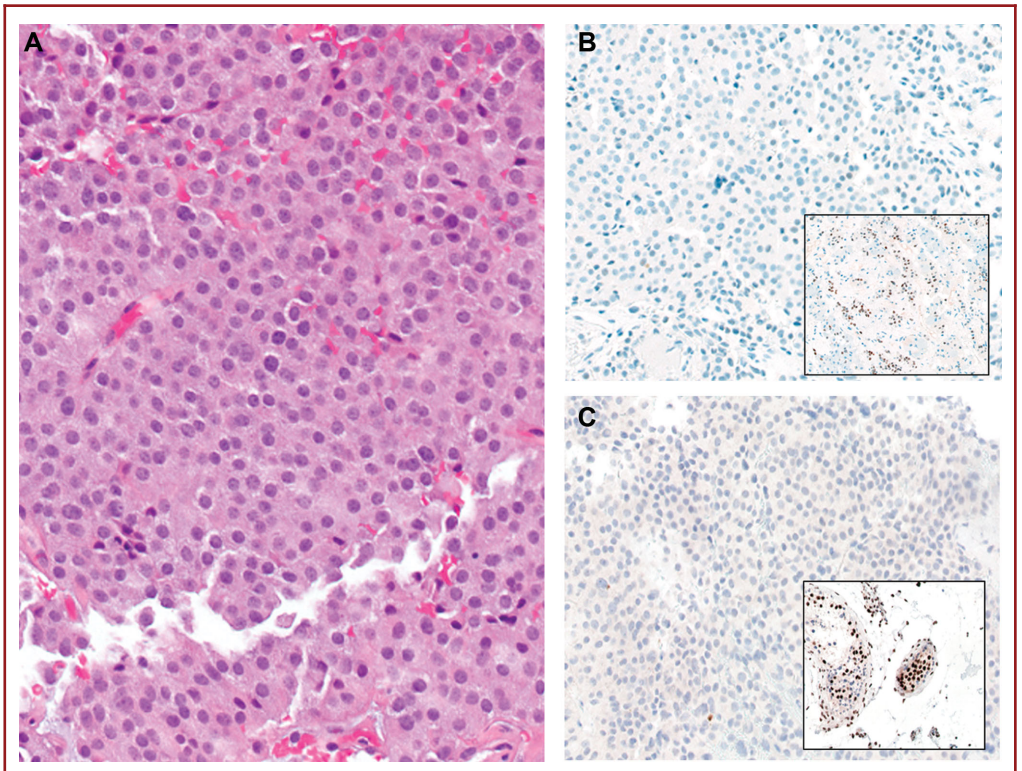


FIGURE 8. *Null cell adenoma.* **A**, *Tumor cells are chromophobic and grow in sheets. Transcription factors PIT-1* **B** *and SF-1* **C** *are completely negative (inset respective positive controls).*

plurihormonal PIT-1 lineage adenomas, an aggressive subtype prone to recurrences and cavernous sinus invasion (Table 2).

In contrast, double adenomas are separate tumors, producing different hormone(s).[55] Rarely, multiple distinct adenomas have been described within the same gland.[55,56] The presence of multiple adenomas may explain cases of surgical failure, in which one or more adenomas are not removed.[56]

Pituitary Carcinoma

Pituitary carcinoma originates from adenohypophyseal cells and comprises ~0.1% to 0.5% of pituitary neoplasms.[5,57,58] Most are hormonally functional tumors of either lactotroph or corticotroph subtype (~two-thirds).[9,59] These malignancies tend to be seen in middle-aged patients (~50-70 yr of age).[59] Most cases are thought to result from transformation of an aggressive pituitary adenoma after a period of multiple latency periods and recurrences.[5,17] The prognosis is poor; mean survival of patients is a few years.[55] Complications from hormone excess also cause morbidity.[56] The tumors tend to be resistant to conventional treatment modalities, though some authors advocate use of temozolomide.[5,8,60]

Microscopically, pituitary carcinoma can appear histologically bland and may be indistinguishable from pituitary adenomas; the diagnosis requires extrapituitary spread of tumor cells (ie, tumor cells present elsewhere in the central nervous system or within systemic organs) (Figure 9A and 9B).[17]

Because of the bland histologic appearance, it is not unusual that some patients receive a diagnosis of pituitary adenoma, and under the later occurrence of metastatic disease, the diagnosis would change to pituitary carcinoma. In an attempt to refine the nomenclature of the pituitary neoplasms following the classification used for neuroendocrine tumors in other organs, the term pituitary neuroendocrine neoplasms was recently suggested.[3,4]

Update on the Pituitary Tumors Nomenclature: PitNETs

"Atypical adenomas" were defined by elevated mitotic index (>2 mitoses per high-power field), positive p53 staining, and Ki67 proliferative index ≥ 3% and were thought to be precursors to pituitary carcinomas because of their aggressive nature. However, the lack of studies to validate this classification especially in recurrence rates created uncertainty about whether "atypical pituitary adenoma" should remain a distinct entity at WHO classification. For this reason, the International Agency for Research on Cancer in 2017 recommended all pituitary tumors be classified as PitNETs rather than adenoma or carcinoma and has been extensively used in the most recent literature.[3,4]

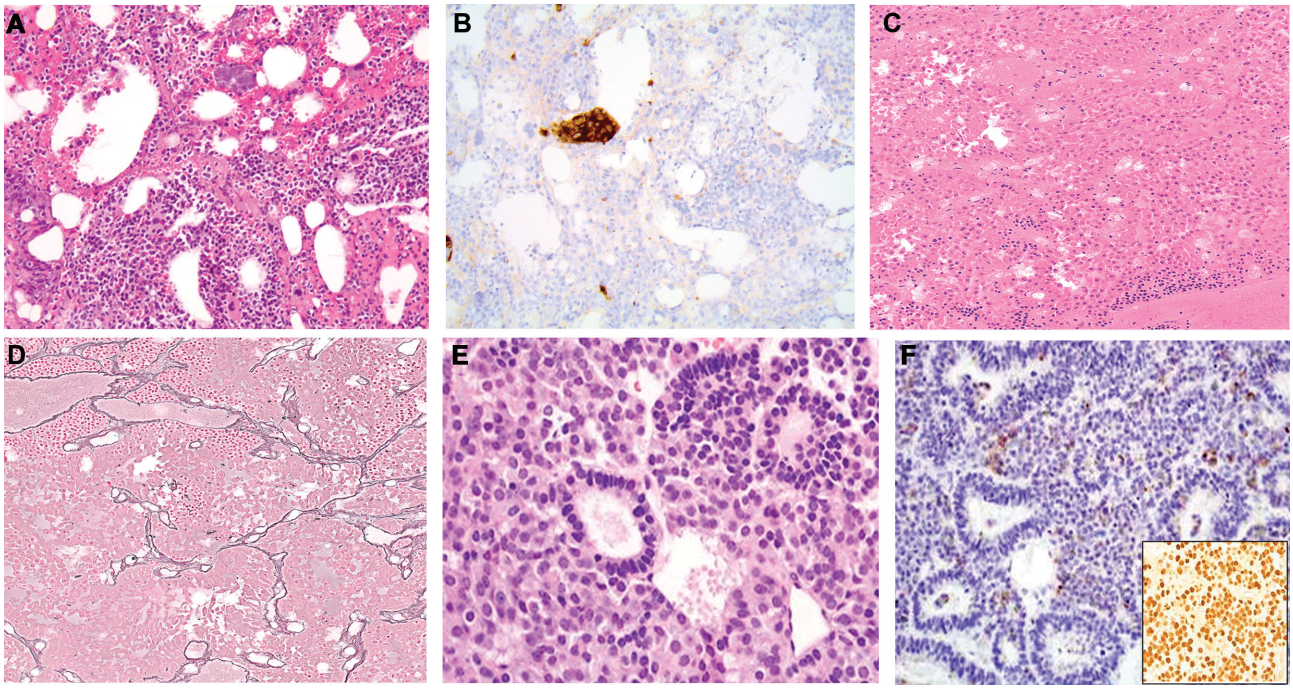


FIGURE 9. **A** *and* **B**, *Pituitary carcinoma.* **A**, *In this bone marrow metastasis, H&E-stained section reveals trilineage hematopoiesis, including many megakaryocytes (circled). Note the bland, cohesive group of epithelioid cells (arrows).* **B**, *These cells stain positive for synaptophysin, a neuroendocrine marker.* **C** *and* **D**, *Pituitary apoplexy.* **C**, *Necrotic adenoma, with preserved cell outlines (coagulative-type necrosis).* **D**, *A reticulin histochemical stain highlights the disrupted and fragmented acinar framework.* **E** *and* **F**, *Pituitary blastoma.* **E**, *On H&E stain, all 3 tumor elements can be seen mixed together: glandular cells, blastemal-like cells, and secretory cells.* **F**, *Scattered cells stain positive with ACTH immunostaining. Inset: T-PIT, a transcription factor for corticotroph adenomas, is positive in tumor cells. Panels* **E** *and* **F** *adapted by permission from Copyright Clearance Center: Springer Nature, Pituitary, Scheithauer et al,*[68] *©2012.*

Pituitary Apoplexy

Pituitary apoplexy is not a separate entity; rather, it is the result of select pituitary adenomas undergoing infarction, with sudden intraglandular hemorrhage. The risk is higher with certain subtypes (especially gonadotroph adenomas) as well as macroadenomas, independent of hormonal production.[8,61] Microscopically, sheets of necrotic epithelioid cells are seen, sometimes with their ghostly outlines still present (Figure 9C). Although immunohistochemistry is often unreliable in necrotic tissue, a reticulin histochemical stain can highlight the adenoma's disrupted and fragmented acinar framework (Figure 9D). The differential diagnosis includes pituitary infarction following pregnancy (Sheehan syndrome) and empty sella syndrome (ESS). Unlike pituitary apoplexy, Sheehan syndrome occurs in the absence of an adenoma.[61] In ESS, ESS volume loss of the pituitary gland occurs, and may arise secondarily because of compression of the gland idiopathically and/or as a result of specific conditions including previous pituitary surgery, radiation therapy of the pituitary region, brain trauma, and pituitary infections.[62-64]

Pituitary Hyperplasia

Pituitary hyperplasia maintains normal connective matrix around expanded acini. Enlarged acini can occur under physiological conditions (ie, prolactin cells in pregnancy), end-organ failure or surgical removal (ie, hypothyroidism), or pathologically (ie, neuroendocrine tumors producing ectopic hypothalamic releasing hormones).[2,8] The gland appears symmetrically involved on both imaging and intraoperative evaluation without a clearly defined lesion.[2] Histopathologically expanded acini are seen unevenly within the gland, usually involving just one cell type.[65] Reticulin staining is necessary to demonstrate the preserved framework.[2] Treatment consists of correcting the underlying endocrine disorder; surgical resection of the neoplasm is recommended in tumor-associated cases.[8,66]

Pituitary Blastoma

Pituitary blastoma is an extremely rare, undifferentiated malignancy of infancy and early childhood,[8,67,68] which recapitulates early developmental adenohypophyseal pituitary gland.[5] The pathogenesis is linked to *DICER1* mutations, an RNase endonuclease on chromosome 14q32.[69] They can manifest in association with other childhood onset tumors, including pineoblastoma and pleuropulmonary blastoma as part of the DICER1 syndrome.[69] Most tumors present clinically with signs of Cushing disease.[12,68]

Histologically, the tumors consist of 3 elements: gland-like structures, larger secretory chromophobic cells, and smaller,

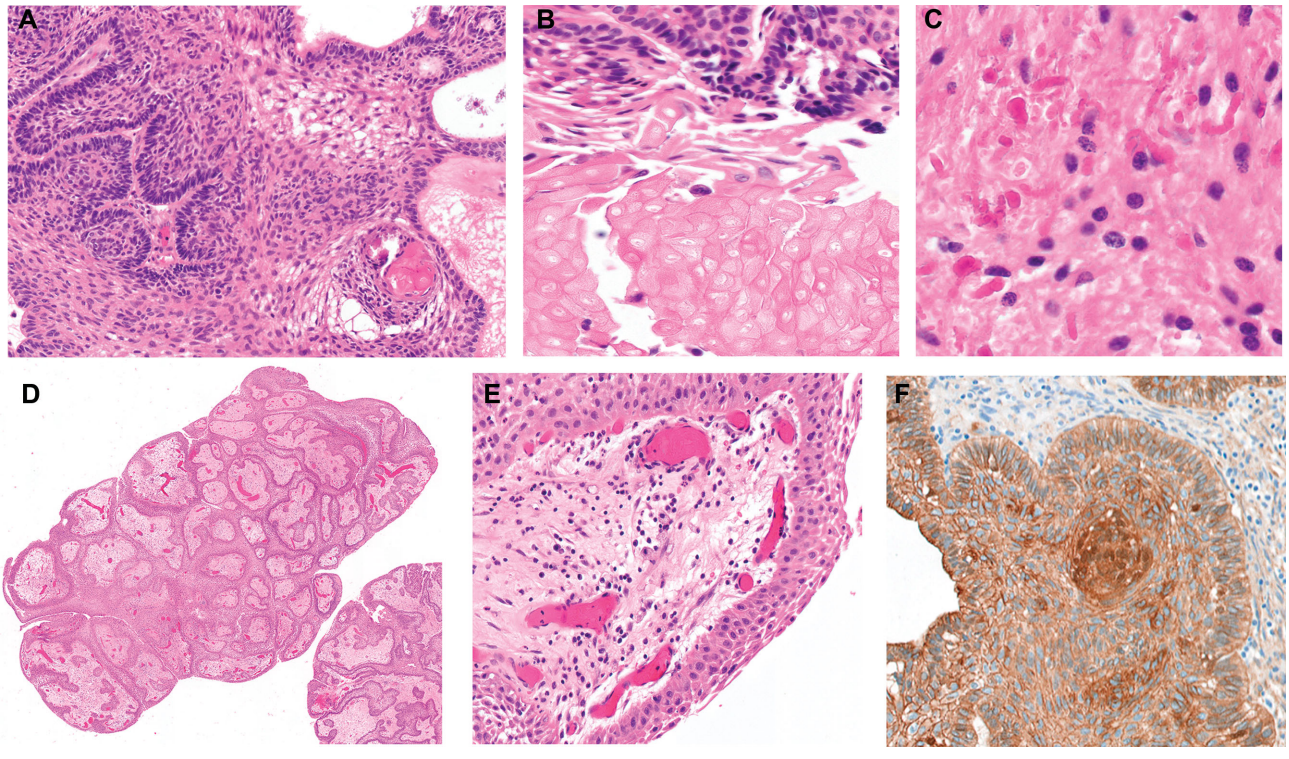


FIGURE 10. *Craniopharyngiomas.* **A-C**, *Adamantinomatous craniopharingioma squamoid nests with peripheral palisading of nuclei and ghost cells (anucleate squamous cells, ie, wet keratin—WK). These tumors press on adjacent structures, inducing a piloid gliosis response with many Rosenthal fibers (arrows).* **D-F**, *Papillary craniopharyngioma.* **D**, *At low power, note the crude papillae (resulting from cellular dehiscence) lined by bland, stratified squamous epithelium.* **E**, *A high-power view. Note the absence of calcifications, wet keratin, or goblet cells.* **F**, *Beta-catenin mutations are detected with nuclear staining at immunohistochemistry. Papillary craniopharyngiomas, which lack these mutations, also lack nuclear staining for beta-cateninin.*

more primitive-appearing blastemal-like cells, likely reflecting the presence of 3 discrete groups of cells in the fetal pituitary (Rathke epithelium, folliculostellate cells, and primitive adenohypophyseal secretory cells) (Figure 9E).[12,68] By immunohistochemistry, the larger secretory cells variably stain for ACTH (Figure 9F).[68] GH staining is seen in rare cells, and positivity for the transcription factor T-Pit is noted (Figure 9F).[68] The prognosis tends to be poor, but because of limited numbers of cases to date,[68] may preclude a definitive clinical picture for this entity. Surgical resection and adjuvant therapy with temozolomide have been attempted.[8]

TUMORS AND CYSTS OF THE PITUITARY REGION

Craniopharyngioma

Craniopharyngiomas originate from Rathke pouch epithelium, part of the developing mouth structures. The 2 histopathological types are adamantinomatous and papillary, which are histologically dissimilar, and also differ in their molecular pathogenesis.

Clinically, both types present with features of a mass lesion; vision changes and headache are common.[12] In children, disruption of the hypothalamic-pituitary network causes endocrine deficiencies (especially of GH secretion), diabetes insipidus, and severe obesity.[12,70,71] Though both are considered benign, they may recur multiple times following subtotal resection. Malignant transformation is rare, and risk factors include radiation therapy and multiple tumor recurrences.[8,72]

Adamantinomatous Craniopharyngioma

Adamantinomatous craniopharyngiomas occur in both children and adults, with peaks at 5 to 10 and 50 to 60 yr of age, respectively.[8] These tumors are driven by *CTNNB1* mutations, detected by β-catenin immunohistochemistry.[71] A solid and cystic tumor, the cyst content often has a dark-brownish color, the so called "motor oil" appearance.[8,12] Yellow-white flecks of cholesterol may be present. Microscopically, squamous nests with peripheral palisading of nuclei, accompanied by variable degrees of anucleate squamous cells ("wet" keratin) and calcifications are noted (Figure 10A and 10B). The appearance is remarkably similar to the related tumors ameloblastoma of the mandible

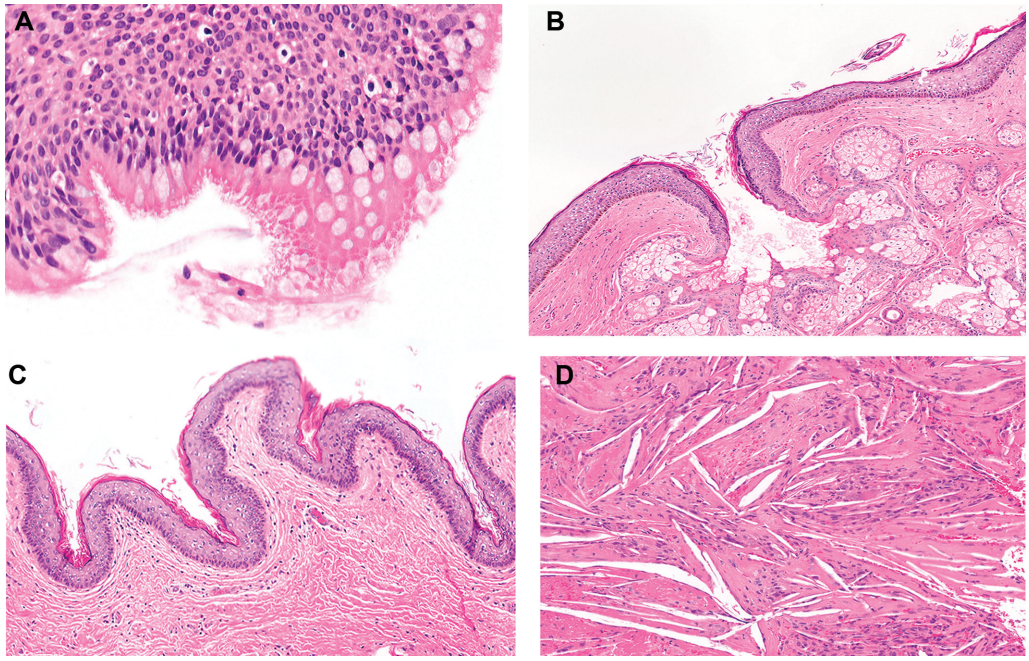


FIGURE 11. *Cystic lesions of the pituitary region.* **A**, *Rathke cleft cyst. Note the cilia and the bluish hue of the goblet cells (here prominent).* **B**, *Dermoid cyst, lined by bland stratified, keratinizing squamous epithelium. Below the surface epithelium are adnexal skin structures (ie, sebaceous glands and hair follicles). Keratin debris composes the cyst contents.* **C**, *Epidermoid cysts appear similar to dermoid cysts, but note the absence of adnexal skin structures.* **D**, *Xanthogranuloma of the sellar region: these reactive processes can result after rupture of a cystic lesion with spilling of contents, typically a Rathke cleft cyst, or an adamantinomatous craniopharyngioma. Note the numerous needle-shaped cleft spaces (cholesterol clefts) and associated giant cell reaction. No epithelium is present.*

and adamantinoma of bone.[43] These craniopharyngiomas are well known to produce piloid gliosis with impressive numbers of Rosenthal fibers in the surrounding brain (Figure 10C); thus, without the squamous nests or other features, pilocytic astrocytoma and other slow-growing tumors enter into the differential diagnosis. Unlike pilocytic astrocytoma, piloid gliosis is not biphasic and also lacks eosinophilic granular bodies (EGBs).[8]

Papillary Craniopharyngioma

These tumors occur almost exclusively in adults (40-50 yr of age).[73] Presenting as solid masses, they lack dark cyst fluid and cholesterol deposits. These tumors sometimes project into the third ventricle and thus enter the differential diagnosis with other intraventricular masses, such as ependymomas and choroid plexus papillomas.[8,74] Microscopically, solid sheets of squamous, nonkeratinizing epithelium forming crude papillae are seen. (Figure 10D-10F)[5,12] Calcifications and "wet" keratin are not present.[75,76] At a molecular level, papillary craniopharyngiomas are characterized by a *BRAF*V600E point mutation; therefore, they may respond to BRAF inhibitors.[75]

Rathke Cleft Cyst

These benign cystic lesions are thought to arise from the intermediate lobe,[1] and present clinically with headaches and visual field changes (Figure 1D).[8] Histologically, the lesion has a thin layer of bland, often ciliated epithelium, occasionally containing goblet cells (Figure 11A). Cyst content, when present, ranges from myxoid/mucoid to eosinophilic and amorphous. The differential diagnosis includes epidermoid/dermoid cysts (Figure 11B and 11C) and papillary craniopharyngioma (Figure 10A), which are solid tumors driven by *BRAF*-V600E mutations, which Rathke cleft cysts lack. Rupture of any of those cysts often results in a xanthogranulomatous inflammatory response (Figure 11D).[8] The prognosis for Rathke cleft cyst is excellent, and although they may recur, complete surgical excision is curative.[8]

TUMORS OF THE NEUROHYPOPHYSIS

Tumors of the neurohypophysis are rare and may cause mass effect symptoms. These tumors are nonendocrine neoplasms; thus, they do not produce pituitary hormones and tend to arise in adults.[77] Absence of expression of synaptophysin and pituitary hormones helps aid in this distinction. Though

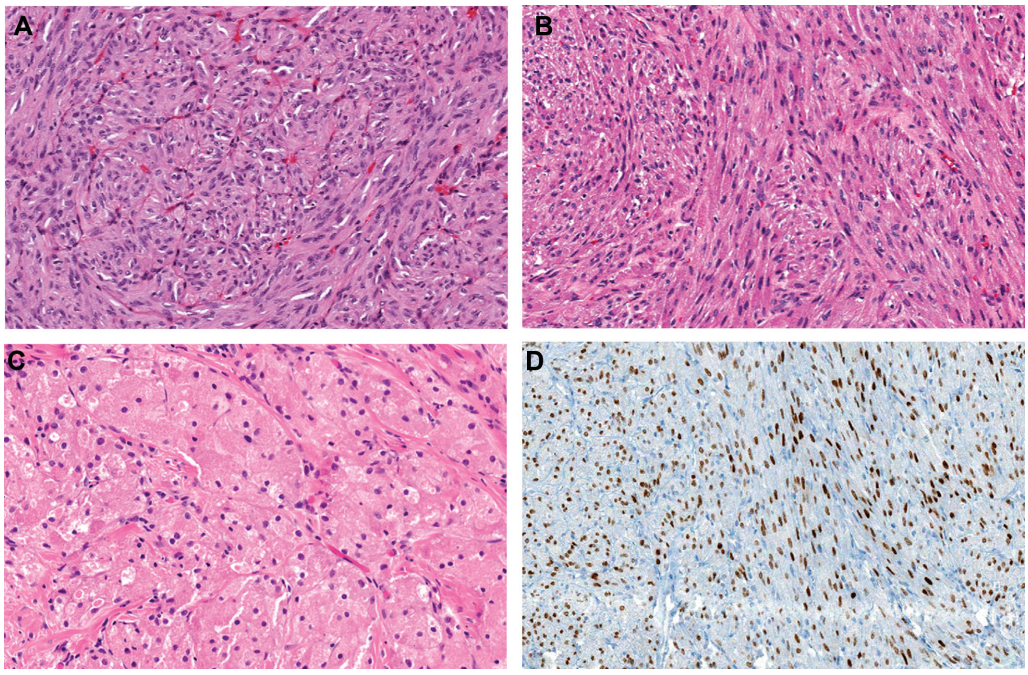


FIGURE 12. *Tumors of the neurohypophysis.* **A**, *Pituicytoma,* **C**, *granular cell tumor,* **B** *and* **D**, *spindle cell oncocytoma, strongly positive for TTF-1, a pattern shared by all 3 entities.*

histologically dissimilar (Figure 12A-12C), they generally share in common benign clinical behavior, as well as expression of thyroid-transcription factor 1 (TTF-1), suggesting a similar precursor cell origin. (Figure 12D)[5,78] Granular cell tumors occur more frequently in females, whereas pituicytoma and spindle cell oncocytoma show no clear gender preference. On imaging, all 3 present similarly as solid, enhancing, well-circumscribed masses often indistinguishable from that of pituitary adenomas.[78]

Pituicytoma

This benign astrocytic neoplasm is histologically composed of bipolar spindle cells arranged in fascicles or storiform patterns (Figure 12A).[79,80] Cytoplasm is abundant and eosinophilic, but not granular. Histochemistry stain with periodic-acid-Schiff (PAS) is negative. The neoplasm lacks Herring bodies (unlike normal neurohypophysis) as well as Rosenthal fibers and EGBs (unlike pilocytic astrocytomas).[8,81,82] S-100 and vimentin are expressed, though Glial Fibrillary acidic protein (GFAP) is variable.[79,80] These tumors do not transform to higher grade, infiltrate, or grow rapidly. Current treatment is surgery.[80,83]

Granular Cell Tumor of the Sellar Region

Though these neoplasms rarely present as a symptomatic mass, they are quite common as an incidental finding at autopsy.[78] Microscopically, cells are epithelioid (discrete cell borders) with abundant, coarsely granular eosinophilic cytoplasm (because of accumulation of lysosomes) and are often arranged in sheets or nodules (Figure 12B).[78] PAS is strongly positive, as well as PAS with diastase digestion (cells are not glycogen-filled).[5] S-100 is generally positive, and GFAP is negative. The tumors grow slowly and are best treated with surgical resection.[78]

Spindle Cell Oncocytoma

These tumors microscopically can display quite variable cell shapes, with epithelioid and spindle cells often mixed, with eosinophilic to oncocytic cytoplasm and usually arranged in fascicles (Figure 12C and 12D).[2,78] The presence of oncocytic changes may lead to an erroneous diagnosis of an oncocytic pituitary adenoma (especially oncocytic null cell pituitary adenoma) without the appropriate immunohistochemical evaluation.[84-86] In contrast to granular cell tumor, cytoplasm is eosinophilic but finely granular (because of accumulation of mitochondria). Staining with PAS is also negative. S-100 is positive, but GFAP is negative. Positive staining for EMA often distinguishes this tumor from pituicytomas and granular cell tumors. Unlike the other diagnostic possibilities of the neurohypophysis, spindle cell oncocytomas can recur in up to 1/3 of cases.[87,88] Usually, recurrent tumors display elevated proliferation indexes and aggressive behavior.[87,89]

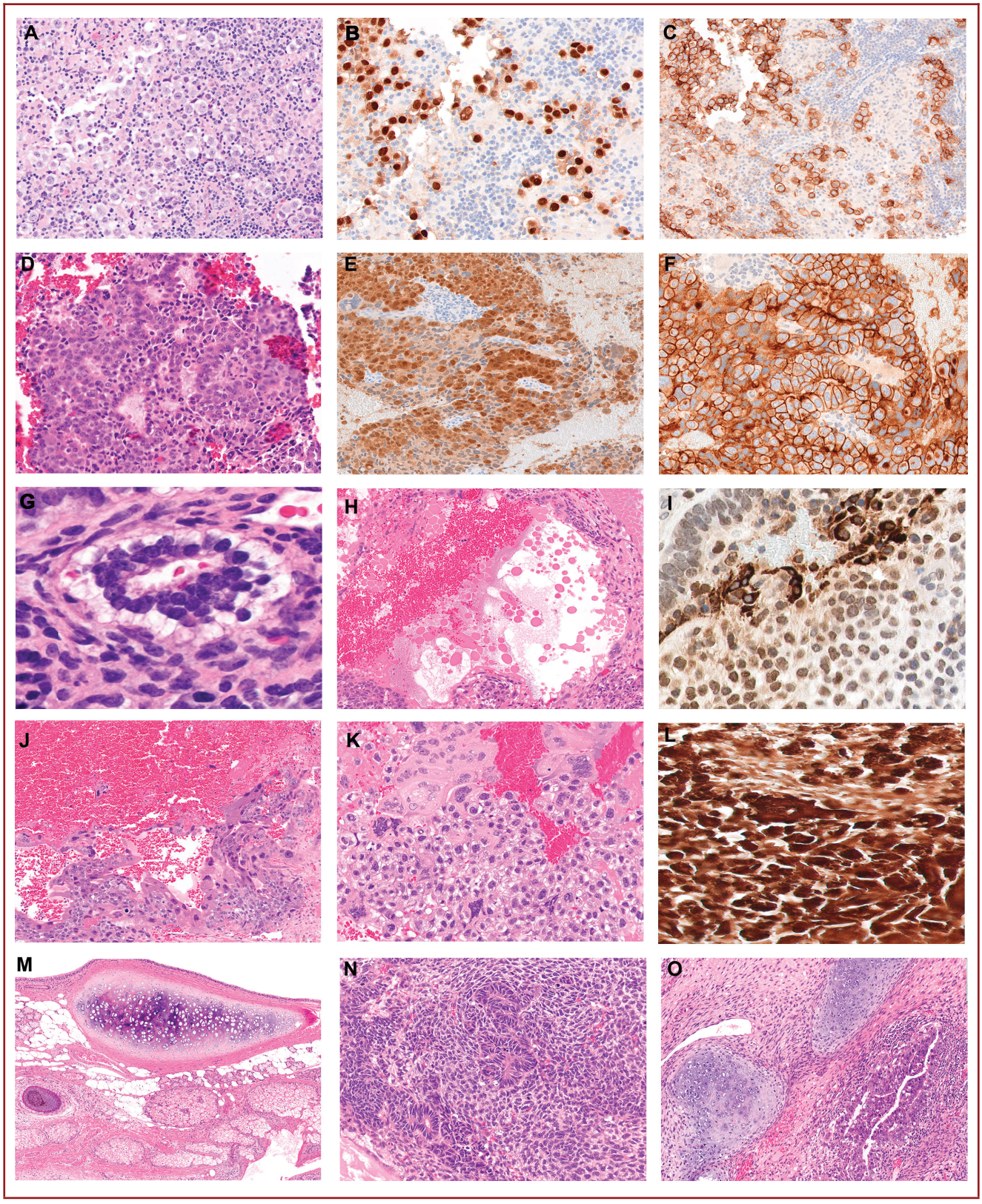


FIGURE 13. *Germ cell tumors of the pituitary.* **A-C**, *Germinoma.* **A**, *Large tumor cells stand out against a background of benign lymphocytes. Sometimes, granulomatous inflammation is so prominent so as to make the tumor cells inconspicuous. Germinomas stain positive with* **B** *OCT3/4 and* **C** *CD117.* **D-F**, *Embryonal carcinoma.* **D**, *These tumors are composed of large, cohesive, pleomorphic cells, often forming gland-like or slit-like spaces. Tumor cells stain with* **E** *CD30 and* **F** *OCT3/4.* **G-I**, *Yolk sac tumor.* **G**, *The characteristic Schiller-Duval body, composed of tumor cells lining a vessel, is not seen in most cases.* **H**, *The reticulated or net-like pattern of growth and hyaline globules may be seen.* **I**, *αFP is positive in the tumor cells.* **J-L**, *Choriocarcinoma.* **J**, *The tumor is composed of a mix of large, multinucleated, often bizarre cells (syncytiotrophoblasts) and smaller, rounded cells, often with cytoplasmic clearing (cytotrophoblasts). The background is often impressively hemorrhagic.* **K**, *Cytotrophoblasts sometimes take on a more "fried egg" appearance.* **L**, *Staining for beta-HCG is intensely positive.* **M** *and* **N**, *Teratoma.* **M**, *Mature teratoma, composed of bland cartilage (C), sebaceous glands (SG), adipose tissue (AT), hair follicle (HF), and respiratory type epithelium.* **N**, *Immature teratoma areas, composed of primitive-appearing cells, sometimes forming rosettes.* **O**, *Mixed germ cell tumor. These neoplasms are composed of varying proportions of 2 or more germ cell subtypes. Here is a combination of teratoma and embryonal carcinoma.*

GERM CELL NEOPLASMS

Similarly, to other midline extragonadal structures, germ cell neoplasms may be seen intracranially. The pituitary region is the second most common site, second to the pineal gland. The majority of cases occur in male adolescents[90,91] and have been described in several genetic syndromes, including Down syndrome, Kleinfelter syndrome, and neurofibromatosis type I.[78] Pure germinoma is the most common germ cell tumor (Figure 13A-13C);[90] infrequent germ cell tumors include embryonal carcinoma (Figure 13D-13F), yolk sac tumor (Figure 13G-13I), choriocarcinoma (Figure 13J-13L), teratoma (Figure 13M and 13N), or mixed germ cell tumors (Figure 13O). Vision changes are a common clinical finding.[78] Specifically, germinomas often cause diabetes insipidus.[8,78]

Germinoma

Germinomas, the intracranial equivalent of seminoma (testes) or dysgerminoma (ovaries), affect male children and adolescents.[78] A higher incidence is seen in East Asia than in people of European origin.[5] Grossly, tumors are solid, tan, and uniform. Histologically, tumor cells are very large with prominent nucleoli and abundant, often clear cytoplasm, often within thin fibrous septae, dividing the tumor into lobules. Benign lymphocytes typically infiltrate the tumor and granulomatous inflammation is notorious (Figure 13A). At its worst, tumor cells may be difficult to perceive and an infectious cause is erroneously sought. By immunohistochemistry, tumor cells are positive for OCT3/4, CD117 (KIT), and PLAP and are negative for cytokeratins and CD30.[43] In pure form, they do not produce alpha-fetoprotein or beta human chorionic gonadotrophin (βHCG). Germinomas have the best prognosis of all germ cell neoplasms. Treatment for germinomas is geared towards radiotherapy, with high cure rates achieved. Nongerminomas tend to be resistant to adjuvant therapy regimens; therefore, gross total resection is the most important factor in prognosis (including for mixed germ cell tumors).[90]

MISCELLANEOUS ADDITIONAL PRIMARY TUMORS OF THE SELLAR REGION

Several distinct and unrelated tumors are also seen in the sellar region. Given the presence of the sellar diaphragm partially encasing the gland, meningeal-based tumors are diagnostic possibilities. Meningioma is the most common meningeal-based tumor and shares features with meningiomas seen elsewhere (Figure 14A). Pilocytic astrocytoma (Figure 14B) may arise in the sellar region and is a differential diagnosis of adamantinomatous craniopharyngioma and pituicytoma.[8,78,81,82] Chordoma can very rarely originate as a primary neoplasm within the dorsum sellae (Figure 14C-14E)[5].

Metastatic Tumors of the Pituitary Region

Metastatic neoplasms to the pituitary are rarely clinically apparent; more commonly, they are found incidentally at autopsy, often in the setting of a systemic malignancy with widespread metastasis.[5] The most common sources are lung and breast tumors. Although lung carcinomas often stain for TTF-1, similar to neurohypophyseal tumors, additional positivity for cytokeratins and napsin A generally excludes tumors of the neurohypophysis (Figure 14F-14H).[78] Metastatic malignancies tend to be more pleomorphic and mitotically active than primary pituitary tumors (ie, pituitary carcinoma), helping to facilitate a correct diagnosis.[5] Composite lesions have also been seen observed involving metastases and pituitary adenomas or craniopharyngiomas.[92]

Inflammatory and Related Lesions of the Pituitary Region

Several distinct inflammatory conditions involve the pituitary gland, including lymphocytic hypophysitis (Figure 15A and 15B), IgG4 disease (Figure 15C and 15D), and Langerhans cell histiocytosis, a clonal lymphoproliferative disorder of histiocytes (activated macrophages), often associated with numerous non-neoplastic inflammatory cells (Figure 15E and 15F).

Lymphocytic Hypophysitis

Lymphocytic hypophysitis is a rare autoimmune disorder wherein a humoral-mediated response results in damage/destruction of the pituitary gland. This disease tends to occur in association with pregnancy; many of the patients have a coexisting autoimmune disorder at the time of diagnosis

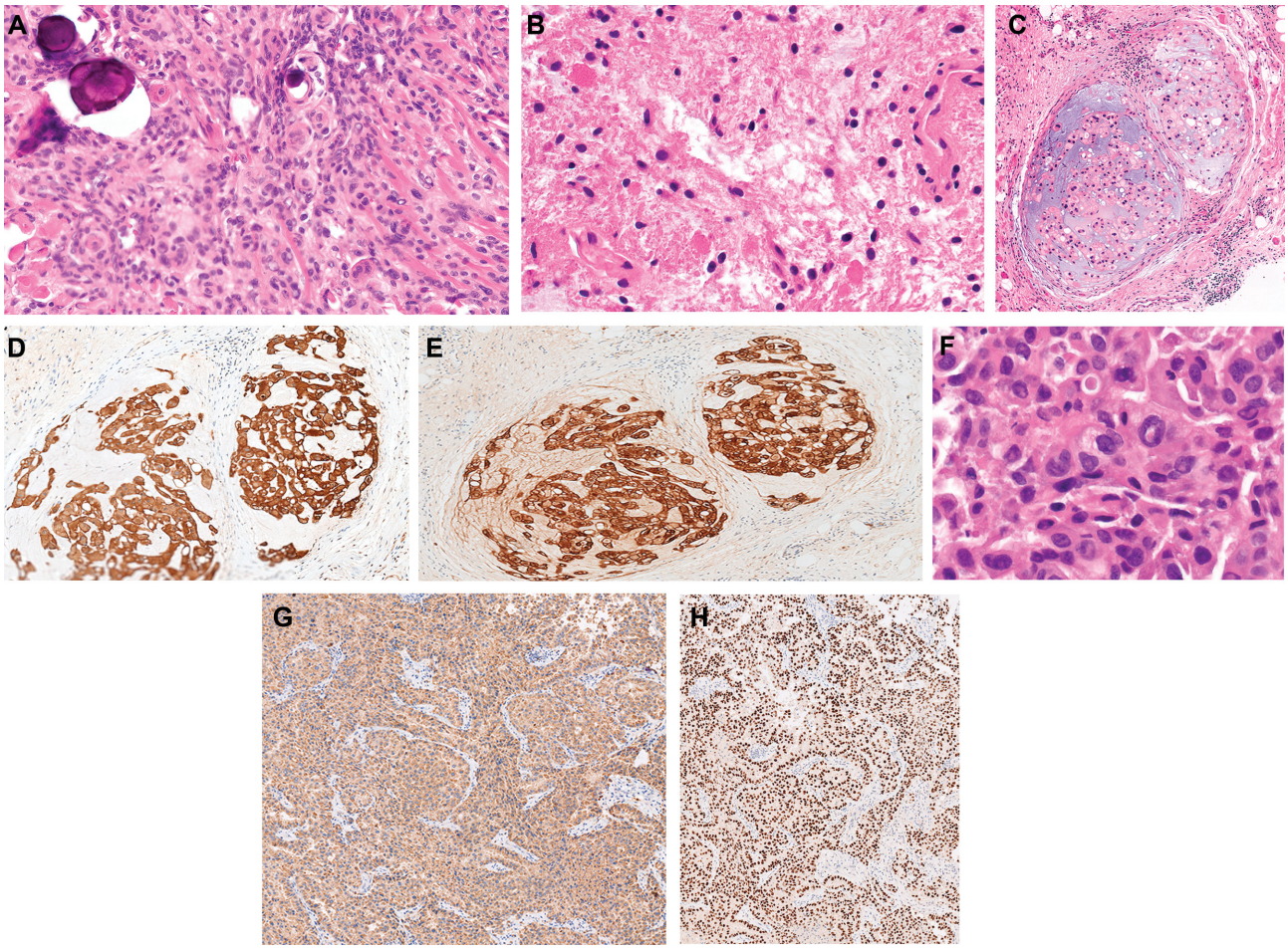


FIGURE 14. *Miscellaneous additional primary tumors of the pituitary region and metastatic malignancies* **A**, *meningioma: cells are arranged syncytially within lobules and whorls. Psammoma bodies (arrows) may be present.* **B**, *Pilocytic astrocytoma: a bland, hypocellular glial neoplasm with numerous eosinophilic granular bodies (EGBs—arrows).* **C**-**E**, *Chordoma.* **C**, *Note the epithelioid cells with abundant, eosinophilic, and bubbly cytoplasm, within a bluish background. Hepatocyte-like chords of epithelioid cells, strung out in a myxoid/mucoid stroma with physaliphorous or bubbly cytoplasm (courtesy of Dr Lawrence Hansen). The main differential diagnosis for chordoma is chondrosarcoma; however, intense and diffuse staining in chordomas for* **D**, *cytokeratin and* **E**, *EMA exclude this as a diagnostic possibility.* **F**-**H**, *Metastatic lung adenocarcinoma.* **F**, *Tumor cells are considerably more pleomorphic and hyperchromatic than expected for pituitary carcinoma. Positivity for* **G**, *napsin A and* **H**, *TTF-1 is seen.*

(ie, thyroiditis).[78] Microscopically, large numbers of mainly T-lymphocytes invade the gland and "attack" the acinar cells (Figure 15A and 15B). Fibrosis eventually occurs in chronic stages, and with enough destruction of the gland, symptoms of hormone deficiency results.[93] Some cases may be IgG4 disease related (Figure 15C and 15D). Treatment consists of steroids and, when necessary, hormone replacement therapy. The prognosis is excellent, with resolution seen postpartum (and only rarely, permanent hypopituitarism).[78]

A possible end stage of lymphocytic hypophysitis is granulomatous hypophysitis.[5,93] Histologically, mixed inflammatory infiltrates, including giant cells and granulomas, beleaguer the gland. Other causes of granulomatous inflammation must be ruled out, including sarcoidosis, or infectious causes, such as fungi and tuberculosis.[5,93]

CONCLUSION

The pituitary and sellar are complex regions affected by multiple inflammatory and neoplastic lesions. Because of the importance of those areas in human metabolism and homeostasis, the consequences of those diseases are usually multisystem. Importantly, neoplastic and non-neoplastic lesions share clinical symptoms and signs, which may be relieved with surgical

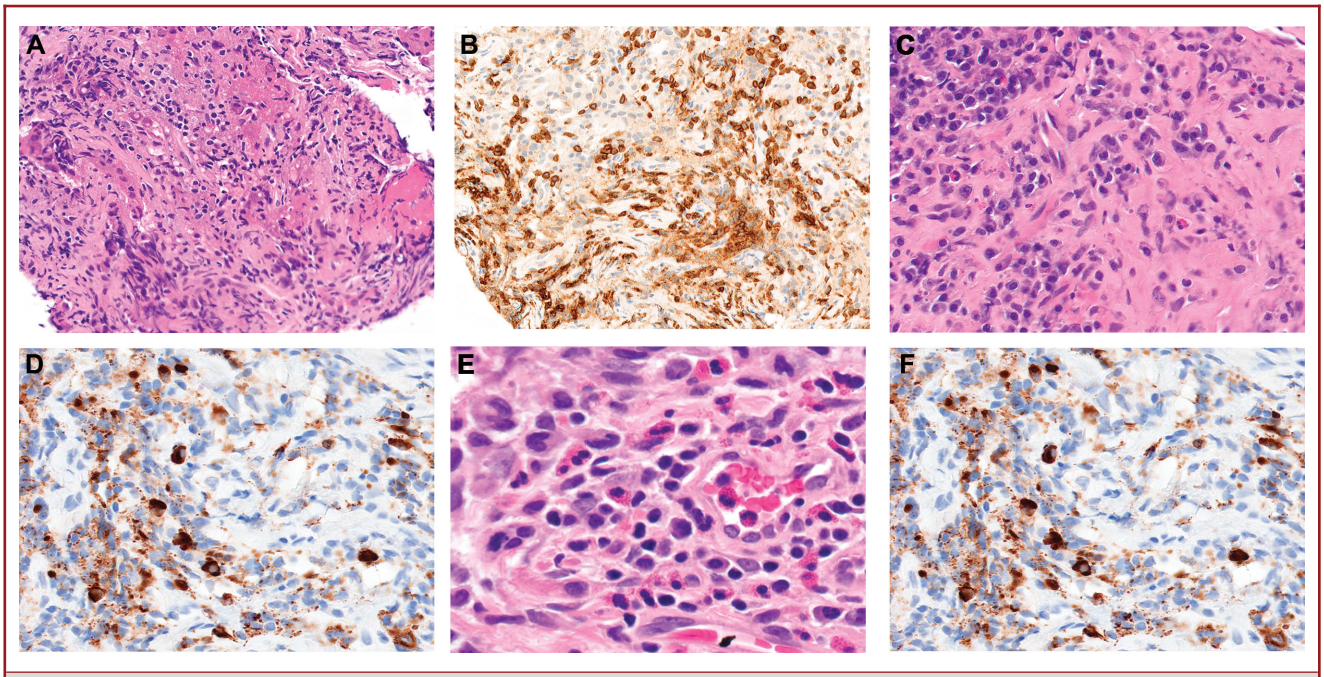


FIGURE 15. *Inflammatory and related lesions of the pituitary region.* **A** *and* **B**, *Lymphocytic hypophysitis.* **A**, *Note acini overrun and engulfed by bland lymphocytes,* **B**, *highlighted with CD3 immunohistochemistry (T-cell marker).* **C** *and* **D**, *IgG4 disease.* **C**, *Note the mixed inflammatory infiltrate (many of which are plasma cells) within a densely fibrotic background.* **D**, *By IHC, plasma cells are often positive for IgG4.* **E** *and* **F**, *Langerhans histiocytosis.* **E**, *On H&E, Langerhans cells have abundant eosinophilic cytoplasm and indented or convoluted nuclei. Here, eosinophils are frequent.* **F**, *CD1a strongly stains the Langerhans cells.*

intervention and specific treatment after histopathological diagnosis by a neuropathologist.

Funding

This study did not receive any funding or financial support.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Brat DJ. *Chapter 1, Neuropathology: A Volume in the Series: Foundations in Diagnostic Pathology*. Elsevier Health Sciences: Philadelphia, PA; 2011.
2. Lopes MBS. The 2017 World Health Organization classification of tumors of the pituitary gland: a summary. *Acta Neuropathol*. 2017;134(4):521-535.
3. Asa SL, Casar-Borota O, Chanson P, et al. From pituitary adenoma to pituitary neuroendocrine tumor (PitNET): an International Pituitary Pathology Club proposal. *Endocr Relat Cancer*. 2017;24(4):C5-C8.
4. Rindi G, Klimstra DS, Abedi-Ardekani B, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod Pathol*. 2018;31(12):1770-1786.
5. Larkin S, Ansorge O. Pathology and pathogenesis of pituitary adenomas and other sellar lesions. In: Feingold KR, Anawalt B, Boyce A, et al. eds. *Endotext*. South Dartmouth, MA, 2000.
6. Gittleman H, Ostrom QT, Farah PD, et al. Descriptive epidemiology of pituitary tumors in the United States, 2004-2009. *J Neurosurg*. 2014;121(3):527-535.
7. Thompson LD, Seethala RR, Muller S. Ectopic sphenoid sinus pituitary adenoma (ESSPA) with normal anterior pituitary gland: a clinicopathologic and immunophenotypic study of 32 cases with a comprehensive review of the English literature. *Head Neck Pathol*. 2012;6(1):75-100.
8. Kleinschmidt-DeMasters BK, Tihan T, Rodriguez F. *Diagnostic Pathology: Neuropathology E-Book*. Elsevier Health Sciences: Salt Lake City, UT; 2016.
9. Lloyd R, Osamura R, Klöppel G, Rosai J. *WHO Classification of Tumours of Endocrine Organs*, 4th ed. vol. 10. Lyon: IARC Press; 2017.
10. Osamura RY, Tahara S, Komatsubara K, et al. Pit-1 positive alpha-subunit positive nonfunctioning human pituitary adenomas: a dedifferentiated GH cell lineage? *Pituitary*. 1999;1(3-4):269-271.
11. Minematsu T, Miyai S, Kajiya H, et al. Recent progress in studies of pituitary tumor pathogenesis. *Endocrine*. 2005;28(1):37-41.
12. Nishioka H, Inoshita N. New WHO classification of pituitary adenomas (4th edition): assessment of pituitary transcription factors and the prognostic histological factors. *Brain Tumor Pathol*. 2018;35(2):57-61.
13. Nishioka H, Inoshita N, Mete O, et al. The complementary role of transcription factors in the accurate diagnosis of clinically nonfunctioning pituitary adenomas. *Endocr Pathol*. 2015;26(4):349-355.
14. Bruno S, Darzynkiewicz Z. Cell cycle dependent expression and stability of the nuclear protein detected by ki-67 antibody in HL-60 cells. *Cell Prolif*. 1992;25(1):31-40.
15. Miermeister CP, Petersenn S, Buchfelder M, et al. Histological criteria for atypical pituitary adenomas—data from the German pituitary adenoma registry suggests modifications. *Acta Neuropathol Commun*. 2015;3:50.
16. Zaidi HA, Cote DJ, Dunn IF, Laws ER Jr. Predictors of aggressive clinical phenotype among immunohistochemically confirmed atypical adenomas. *J Clin Neurosci*. 2016;34:246-251.
17. Mete O, Lopes MB. Overview of the 2017 WHO classification of pituitary tumors. *Endocr Pathol*. 2017;28(3):228-243.
18. Akirov A, Asa SL, Amer L, Shimon I, Ezzat S. The clinicopathological spectrum of acromegaly. *J Clin Med*. 2019;8(11).
19. Eugster E. Gigantism. In: Feingold KR, Anawalt B, Boyce A, et al. eds. *Endotext*. South Dartmouth, MA; 2000.

20. Beckers A, Petrossians P, Hanson J, Daly AF. The causes and consequences of pituitary gigantism. *Nat Rev Endocrinol*. 2018;14(12):705-720.
21. Pereira BD, Raimundo L, Mete O, Oliveira A, Portugal J, Asa SL. Monomorphous plurihormonal pituitary adenoma of pit-1 lineage in a giant adolescent with central hyperthyroidism. *Endocr Pathol*. 2016;27(1):25-33.
22. Kiseljak-Vassiliades K, Carlson NE, Borges MT, et al. Growth hormone tumor histological subtypes predict response to surgical and medical therapy. *Endocrine*. 2015;49(1):231-241.
23. Trouillas J, Jaffrain-Rea ML, Vasiljevic A, Raverot G, Roncaroli F, Villa C. How to classify the pituitary neuroendocrine tumors (PitNET)s in 2020. *Cancers*. 2020;12(2):514. 1-17.
24. Mete O, Asa SL. Therapeutic implications of accurate classification of pituitary adenomas. *Semin Diagn Pathol*. 2013;30(3):158-164.
25. Teramoto S, Tange Y, Ishii H, Goto H, Ogino I, Arai H. Mixed gangliocytoma-pituitary adenoma containing GH and GHRH co-secreting adenoma cells. *Endocrinol Diabetes Metab Case Rep*. 2019;2019:19-0099.
26. Lee MH, McKelvie P, Krishnamurthy B, Wang YY, Caputo C. An intrasellar pituitary adenoma-gangliocytoma presenting as acromegaly. *Endocrinol Diabetes Metab Case Rep*. 2017;2017:17-0035.
27. Agustsson TT, Baldvinsdottir T, Jonasson JG, et al. The epidemiology of pituitary adenomas in Iceland, 1955–2012: a nationwide population-based study. *Eur J Endocrinol*. 2015;173(5):655-664.
28. Delgrange E, Vasiljevic A, Wierinckx A, et al. Expression of estrogen receptor alpha is associated with prolactin pituitary tumor prognosis and supports the sex-related difference in tumor growth. *Eur J Endocrinol*. 2015;172(6):791-801.
29. Mete O, Asa SL. Clinicopathological correlations in pituitary adenomas. *Brain Pathol*. 2012;22(4):443-453.
30. Levine SN, Ishaq S, Nanda A, Wilson JD, Gonzalez-Toledo E. Occurrence of extensive spherical amyloid deposits in a prolactin-secreting pituitary macroadenoma: a radiologic-pathologic correlation. *Ann Diagn Pathol*. 2013;17(4):361-366.
31. Gul S, Bahadir B, Dusak A, Kalayci M, Edebali N, Acikgoz B. Spherical amyloid deposition in a prolactin-producing pituitary adenoma. *Neuropathology*. 2009;29(1):81-84.
32. Chatzellis E, Alexandraki KI, Androulakis II, Kaltsas G. Aggressive pituitary tumors. *Neuroendocrinology*. 2015;101(2):87-104.
33. Lopes MBS. Pathology of prolactinomas: any predictive value? *Pituitary*. 2020;23(1):3-8.
34. Smith TR, Hulou MM, Huang KT, et al. Current indications for the surgical treatment of prolactinomas. *J Clin Neurosci*. 2015;22(11):1785-1791.
35. Donegan D, Atkinson JL, Jentoft M, et al. Surgical outcomes of prolactinomas in recent era: results of a heterogenous group. *Endocr Pract*. 2017;23(1):37-45.
36. Perry A, Graffeo CS, Marcellino C, Pollock BE, Wetjen NM, Meyer FB. Pediatric pituitary adenoma: case series, review of the literature, and a skull base treatment paradigm. *J Neurol Surg B Skull Base*. 2018;79(1):91-114.
37. Yamada S, Inoshita N, Fukuhara N, et al. Therapeutic outcomes in patients undergoing surgery after diagnosis of Cushing's disease: a single-center study. *Endocr J*. 2015;62(12):1115-1125.
38. Sun Y, Sun Q, Fan C, et al. Diagnosis and therapy for Cushing's disease with negative dynamic MRI finding: a single-centre experience. *Clin Endocrinol*. 2012;76(6):868-876.
39. Prevedello DM, Pouratian N, Sherman J, et al. Management of Cushing's disease: outcome in patients with microadenoma detected on pituitary magnetic resonance imaging. *J Neurosurg*. 2008;109(4):751-759.
40. Ben-Shlomo A, Cooper O. Silent corticotroph adenomas. *Pituitary*. 2018;21(2):183-193.
41. Todnem N, Ward A, Segar S, Rojiani AM, Rahimi SY. Clinically silent adrenocorticotropic hormone-positive crooke cell adenoma: case report and review of literature. *World Neurosurg*. 2018;119:197-200.
42. Pivonello R, De Leo M, Cozzolino A, Colao A. The treatment of Cushing's disease. *Endocr Rev*. 2015;36(4):385-486.
43. Cheng L, Bostwick DG. *Essentials of Anatomic Pathology*. Springer Science & Business Media: NY, NY; 2011.
44. Sun T, Liu L, Sunnassee A, Zhuo L, Zhu S. Sudden death in custody due to pituitary apoplexy during long restriction in a sitting position: a case report and review of the literature. *J Forensic Leg Med*. 2013;20(7):812-815.
45. Kessel KA, Diehl CD, Oechsner M, et al. Patient-reported outcome (PRO) as an addition to long-term results after high-precision stereotactic radiotherapy in patients with secreting and non-secreting pituitary adenomas: a retrospective cohort study up to 17-years follow-up. *Cancers*. 2019;11(12):1884. 1-14.
46. Mehta GU, Lonser RR. Management of hormone-secreting pituitary adenomas. *Neuro Oncol*. 2017;19(6):762-773.
47. Yamada S, Fukuhara N, Horiguchi K, et al. Clinicopathological characteristics and therapeutic outcomes in thyrotropin-secreting pituitary adenomas: a single-center study of 90 cases. *J Neurosurg*. 2014;121(6):1462-1473.
48. Varlamov EV, McCartney S, Fleseriu M. Functioning pituitary adenomas—current treatment options and emerging medical therapies. *Eur Endocrinol*. 2019;15(1):30-40.
49. Balogun JA, Monsalves E, Juraschka K, et al. Null cell adenomas of the pituitary gland: an institutional review of their clinical imaging and behavioral characteristics. *Endocr Pathol*. 2015;26(1):63-70.
50. Ntali G, Wass JA. Epidemiology, clinical presentation and diagnosis of non-functioning pituitary adenomas. *Pituitary*. 2018;21(2):111-118.
51. Mete O, Cintosun A, Pressman I, Asa SL. Epidemiology and biomarker profile of pituitary adenohypophysial tumors. *Mod Pathol*. 2018;31(6):900-909.
52. Kontogeorgos G, Thodou E. The gonadotroph origin of null cell adenomas. *Hormones*. 2016;15(2):243-247.
53. Liu J, He Y, Zhang X, Yan X, Huang Y. Clinicopathological analysis of 250 cases of pituitary adenoma under the new WHO classification. *Oncol Lett*. 2020;19(3):1890-1898.
54. Serioli S, Doglietto F, Fiorindi A, et al. Pituitary adenomas and invasiveness from anatomo-surgical, radiological, and histological perspectives: a systematic literature review. *Cancers*. 2019;11(12):1936. 1-21.
55. Hansen TM, Batra S, Lim M, et al. Invasive adenoma and pituitary carcinoma: a SEER database analysis. *Neurosurg Rev*. 2014;37(2):279-285; discussion 285-276.
56. Heaney A. Management of aggressive pituitary adenomas and pituitary carcinomas. *J Neurooncol*. 2014;117(3):459-468.
57. Heaney AP. Clinical review: pituitary carcinoma: difficult diagnosis and treatment. *J Clin Endocrinol Metab*. 2011;96(12):3649-3660.
58. Saeger W, Ludecke DK, Buchfelder M, Fahlbusch R, Quabbe HJ, Petersenn S. Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. *Eur J Endocrinol*. 2007;156(2):203-216.
59. Carey RM, Kuan EC, Workman AD, et al. A population-level analysis of pituitary carcinoma from the national cancer database. *J Neurol Surg B Skull Base*. 2020;81(2):180-186.
60. Lim S, Shahinian H, Maya MM, Yong W, Heaney AP. Temozolomide: a novel treatment for pituitary carcinoma. *Lancet Oncol*. 2006;7(6):518-520.
61. Tanriverdi F, Dokmetas HS, Kebapci N, et al. Etiology of hypopituitarism in tertiary care institutions in Turkish population: analysis of 773 patients from Pituitary Study Group database. *Endocrine*. 2014;47(1):198-205.
62. Lenz AM, Root AW. Empty sella syndrome. *Pediatr Endocrinol Rev*. 2012;9(4):710-715.
63. Ouma J. Primary empty sella syndrome associated with visual deterioration salvaged by chiasmapexy: report of a case and discussion of the literature. *Surg Neurol Int*. 2020;11:48.
64. Chiloiro S, Giampietro A, Bianchi A, et al. Diagnosis of endocrine disease: primary empty sella: a comprehensive review. *Eur J Endocrinol*. 2017;177(6):R275-R285.
65. Horvath E, Kovacs K, Scheithauer BW. Pituitary hyperplasia. *Pituitary*. 1999;1(3-4):169-179.
66. Shivaprasad KS, Siddardha K. Pituitary hyperplasia from primary hypothyroidism. *N Engl J Med*. 2019;380(8):e9.
67. de Kock L, Sabbaghian N, Plourde F, et al. Pituitary blastoma: a pathognomonic feature of germ-line DICER1 mutations. *Acta Neuropathol*. 2014;128(1):111-122.
68. Scheithauer BW, Horvath E, Abel TW, et al. Pituitary blastoma: a unique embryonal tumor. *Pituitary*. 2012;15(3):365-373.
69. Herriges JC, Brown S, Longhurst M, et al. Identification of two 14q32 deletions involving DICER1 associated with the development of DICER1-related tumors. *Eur J Med Genet*. 2019;62(1):9-14.
70. Bogusz A, Muller HL. Childhood-onset craniopharyngioma: latest insights into pathology, diagnostics, treatment, and follow-up. *Expert Rev Neurother*. 2018;18(10):793-806.
71. Muller HL. Risk-adapted, long-term management in childhood-onset craniopharyngioma. *Pituitary*. 2017;20(2):267-281.
72. Gao S, Shi X, Wang Y, Qian H, Liu C. Malignant transformation of craniopharyngioma: case report and review of the literature. *J Neurooncol*. 2011;103(3):719-725.

73. Pekmezci M, Louie J, Gupta N, Bloomer MM, Tihan T. Clinicopathological characteristics of adamantinomatous and papillary craniopharyngiomas: University of California, San Francisco experience 1985-2005. *Neurosurgery*. 2010;67(5):1341-1349; discussion 1349.
74. Ahmed SI, Javed G, Laghari AA, et al. Third ventricular tumors: a comprehensive literature review. *Cureus*. 2018;10(10):e3417.
75. Larkin S, Karavitaki N. Recent advances in molecular pathology of craniopharyngioma. *F1000Res*. 2017;6:1202.
76. Brastianos PK, Shankar GM, Gill CM, et al. Dramatic response of BRAF V600E mutant papillary craniopharyngioma to targeted therapy. *J Natl Cancer Inst*. 2019;108(2):1-5.
77. Mete O, Lopes MB, Asa SL. Spindle cell oncocytomas and granular cell tumors of the pituitary are variants of pituicytoma. *Am J Surg Pathol*. 2013;37(11):1694-1699.
78. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol*. 2007;114(2):97-109.
79. Borg A, Jaunmuktane Z, Dorward N. Tumors of the neurohypophysis: one unit's experience and literature review. *World Neurosurg*. 2020;134:e968-e978.
80. Guerrero-Perez F, Vidal N, Marengo AP, et al. Posterior pituitary tumours: the spectrum of a unique entity. A clinical and histological study of a large case series. *Endocrine*. 2019;63(1):36-43.
81. Parish JM, Bonnin JM, Payner TD, Goodman JM, Cohen-Gadol AA. Intrasellar pilocytic astrocytomas: clinical, imaging, pathological, and surgical findings. *J Clin Neurosci*. 2015;22(4):653-658.
82. Prashant Prasad G, Lang FF, Bruner JM, Ater JL, McCutcheon IE. Transsphenoidal removal of intrasellar pilocytic astrocytoma. *J Clin Neurosci*. 2014;21(6):1047-1048.
83. Feng M, Carmichael JD, Bonert V, Bannykh S, Mamelak AN. Surgical management of pituicytomas: case series and comprehensive literature review. *Pituitary*. 2014;17(5):399-413.
84. Vajtai I, Sahli R, Kappeler A. Spindle cell oncocytoma of the adenohypophysis: report of a case with a 16-year follow-up. *Pathol Res Pract*. 2006;202(10):745-750.
85. Matyja E, Maksymowicz M, Grajkowska W, Olszewski W, Zielinski G, Bonicki W. Spindle cell oncocytoma of the adenohypophysis—a clinicopathological and ultrastructural study of two cases. *Folia Neuropathol*. 2010;48(3):175-184.
86. Romero-Rojas AE, Melo-Uribe MA, Barajas-Solano PA, Chinchilla-Olaya SI, Escobar LI, Hernandez-Walteros DM. Spindle cell oncocytoma of the adenohypophysis. *Brain Tumor Pathol*. 2011;28(4):359-364.
87. Mu Q, Yu J, Qu L, et al. Spindle cell oncocytoma of the adenohypophysis: two case reports and a review of the literature. *Mol Med Rep*. 2015;12(1):871-876.
88. Billeci D, Marton E, Giordan E, Carraro V, Ronzon M, Rossi S. Spindle cell oncocytoma: report of two cases with massive bleeding and review of the literature. *J Clin Neurosci*. 2017;39:39-44.
89. Borota OC, Scheithauer BW, Fougner SL, Hald JK, Ramm-Pettersen J, Bollerslev J. Spindle cell oncocytoma of the adenohypophysis: report of a case with marked cellular atypia and recurrence despite adjuvant treatment. *Clin Neuropathol*. 2009;28(2):91-95.
90. Takami H, Perry A, Graffeo CS, et al. Comparison on epidemiology, tumor location, histology, and prognosis of intracranial germ cell tumors between Mayo Clinic and Japanese consortium cohorts. *J Neurosurg*. 2020:1-11.
91. Ho DM, Liu HC. Primary intracranial germ cell tumor. Pathologic study of 51 patients. *Cancer*. 1992;70(6):1577-1584.
92. Helton M, Abu-Rmaileh M, Thomas K, Gokden M, Kanaan A, Rodriguez A. Pituitary metastatic composite tumors: a case report with next-generation sequencing and review of the literature. *Case Rep Oncol Med*. 2020;2020:5073236.
93. Elgamal ME, Mohamed RMH, Fiad T, Elgamal EA. Granulomatous hypophysitis: rare disease with challenging diagnosis. *Clin Case Rep*. 2017;5(7):1147-1151.

Acknowledgments

We thank Diana Thomas, MD, PhD, Assistant Professor Department of Neuropathology, OSU, for providing several of the case pictures illustrating this paper. We also thank Rick Marshall, Senior Systems Manager, and Keith Mullins, Wexner Medical Center (WMC) Senior Systems Consultant/Epic Beaker, for the support on cases selection and searches at the Pathology digital files at OSU. And we thank Scott Hammond, Lead Digital Pathology Specialist, Digital Pathology Core, OSU-WMC, and David Kellough, Virtual Microscopy/Image Analysis Technician at OSU-WMC, for their support in making the TIFF files.