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Overview of the 2022 WHO Classification of Pituitary Tumors

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Abstract

This review summarizes the changes in the 5th Edition of the WHO Classification of Endocrine and Neuroendocrine Tumors that relate to the pituitary gland. The new classification clearly distinguishes anterior lobe (adenohypophyseal) from posterior lobe (neurohypophyseal) and hypothalamic tumors. Other tumors arising in the sellar region are also discussed. Anterior lobe tumors include (i) well-differentiated adenohypophyseal tumors that are now classified as pituitary neuroendocrine tumors (PitNETs; formerly known as pituitary adenomas), (ii) pituitary blastoma, and (iii) the two types of craniopharyngioma. The new WHO classification provides detailed histological subtyping of a PitNET based on the tumor cell lineage, cell type, and related characteristics. The routine use of immunohistochemistry for pituitary transcription factors (PIT1, TPIT, SF1, GATA3, and ERα) is endorsed in this classification. The major PIT1, TPIT, and SF1 lineage-defined PitNET types and subtypes feature distinct morphologic, molecular, and clinical differences. The "null cell" tumor, which is a diagnosis of exclusion, is reserved for PitNETs with no evidence of adenohypophyseal lineage differentiation. Unlike the 2017 WHO classification, mammosomatotroph and acidophil stem cell tumors represent distinct PIT1-lineage PitNETs. The diagnostic category of PIT1-positive plurihormonal tumor that was introduced in the 2017 WHO classification is replaced by two clinicopathologically distinct PitNETs: the immature PIT1-lineage tumor (formerly known as silent subtype 3 tumor) and the mature plurihormonal PIT1-lineage tumor. Rare unusual plurihormonal tumors feature multi-lineage differentiation. The importance of recognizing multiple synchronous PitNETs is emphasized to avoid misclassification. The term "metastatic PitNET" is advocated to replace the previous terminology "pituitary carcinoma" in order to avoid confusion with neuroendocrine carcinoma (a poorly differentiated epithelial neuroendocrine neoplasm). Subtypes of PitNETs that are associated with a high risk of adverse biology are emphasized within their cell lineage and cell type as well as based on clinical variables. Posterior lobe tumors, the family of pituicyte tumors, include the traditional pituicytoma, the oncocytic form (spindle cell oncocytoma), the granular cell form (granular cell tumor), and the ependymal type (sellar ependymoma). Although these historical terms are entrenched in the literature, they are nonspecific and confusing, such that oncocytic pituicytoma, granular cell pituicytoma, and ependymal pituicytoma are now proposed as more accurate. Tumors with hypothalamic neuronal differentiation are classified as gangliocytomas or neurocytomas based on large and small cell size, respectively. This classification sets the standard for a high degree of sophistication to allow individualized patient management approaches.

Keywords Pituitary neuroendocrine tumor · Pituitary adenoma · PitNET · Pituitary blastoma · Craniopharyngioma · Pituicytoma · Gangliocytoma · Neurocytoma

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Introduction

The pituitary is a complex organ that is composed of adenohypophyseal hormone-secreting neuroendocrine cells, posterior lobe pituicytes that are modified glia, axonal extensions of hypothalamic neurons that secrete hormones into the bloodstream, and stromal cells that include blood vessels, nerves, meninges, bone, and other connective tissue elements [1]. The sella turcica is the site of tumors that arise from all of these various cell types. Because of the fascination with hormone excess syndromes, such as acromegaly, Cushing disease, central hyperthyroidism, and hyperprolactinemia, pituitary tumor studies have mainly focused on hormone production. However, the development of molecular tools that facilitate better understanding of the mechanisms responsible for cell differentiation has provided further clarity, and the field has advanced significantly over the last 20 years [2]. It is now clear that there are specific cell lineages that are terminally differentiated, while other cell types are more fluid, providing access to transdifferentiation [3–5] as required for changes in physiology.

The 5th edition of the WHO Classification of Endocrine and Neuroendocrine Tumors has made significant advances in recognizing the progress made by the application of advanced tools to characterize tumors of the sellar region beyond the conventional hormonal activity that has been the basis for classification in past editions. Tumors are now classified based on cell lineage as determined by expression of transcription factors, hormones, and other biomarkers. As with the other 5th edition WHO series, a specific tumor entity is now referred to as a tumor "type," whereas variants are considered "subtypes."

In this review, we adopt a question–answer model to summarize the most important changes that will allow more accurate classification, better understanding of molecular and functional implications, and as a consequence, a more targeted approach to therapy.

Question 1: What Is the Significance of the Nomenclature Change from Pituitary Adenoma to Pituitary Neuroendocrine Tumor? What Happened to Pituitary Carcinoma?

A major nomenclature change from the previous edition of the WHO classification is the transition from "adenoma" to "pituitary neuroendocrine tumor" (PitNET). The hormone-secreting cells of the adenohypophysis are neuroendocrine cells and their tumors are therefore neuroendocrine neoplasms [6]. They have for many years been classified as adenomas based on the rarity of metastatic behavior. However, adenomas are, by definition, benign, and benign implies a disease that is not harmful, which does not threaten health or life and that has no significant impact on the host. These are not features of a significant number of pituitary tumors. In fact, pituitary tumors are often invasive neoplasms that can infiltrate into surrounding structures, not unlike carcinomas. Moreover, when they do metastasize, there are no morphologic or molecular features that can predict metastatic spread; using traditional nomenclature, the initial diagnosis is "adenoma" and only when the metastasis is identified is the diagnosis changed to "carcinoma." It should be clear that there is no such thing as a metastasizing adenoma; therefore, the term is not appropriate for tumors of adenohypophyseal cells. Another important point is that the approach to management of unresectable pituitary tumors involves the same therapies as used for neuroendocrine tumors in other sites.

Based on these many issues in pituitary pathology, a proposal was made to rename these lesions PitNETs [7]. This approach fits well with the aim to provide a uniform classification system for all neuroendocrine neoplasms (NENs) [8]. This classification divides epithelial NENs into well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). Since PitNETs can have metastases and since even metastatic lesions generally do not become poorly differentiated, there is no rationale to use the term "carcinoma"; instead, one can now classify PitNETs as primary and metastatic lesions. Sometimes, NETs from extra-pituitary sites such as pancreas or the digestive system may metastasize to the pituitary and mimic the histology of PitNET [9–11]; the correct diagnosis requires the use of pituitary transcription factors to ensure that PitNETs are distinguished from other NETs [12].

Question 2: What Are the New Diagnostic Categories of Pituitary Neuroendocrine Tumors?

The new classification, summarized in Table 1, places an emphasis on the various cell types and their subtypes, as well as on tumors that do not show features of normal cell differentiation. The adenohypophysis is composed of at least six normal cell types: somatotrophs, lactotrophs, mammosomatotrophs, and thyrotrophs are of PIT1 lineage, corticotrophs are of TPIT lineage, and gonadotrophs are of SF1 lineage. In the previous 2017 WHO classification, mammosomatotroph tumors were not classified as a distinct type, but in the new edition, they assume a position of relevance.

Table 1 The 2022 WHO classification of pituitary neuroendocrine tumors (PitNETs)

PitNET Type	Subtype	Transcription factors	Hormones	LMWK
PIT1-lineage PitNETs				
Somatotroph tumors	Densely granulated somatotroph tumor	PIT1	GH, α-subunit	Perinuclear
	Sparsely granulated somatotroph tumor	PIT1	GH	Fibrous bodies (> 70%)
Lactotroph tumors	Sparsely granulated lactotroph tumor	PIT1, ERα	PRL (paranuclear dot-like)	Weak or negative
	Densely granulated lactotroph tumor		PRL (diffuse cytoplasmic)	Weak or negative
Mammosomatotroph tumor		PIT1, ERα	GH (predominant), PRL, α-subunit	Perinuclear
Thyrotroph tumor		PIT1, GATA3	α-subunit, βTSH	Weak or negative
Mature plurihormonal PIT1-lineage tumor		PIT1, ERα, GATA3	Monomorphic tumor cells with predominant GH expression and variable PRL, βTSH, and α-subunit	Perinuclear
Immature PIT1-lineage tumor		PIT1 (ERα, GATA3)	Monomorphic tumor cells with focal/variable staining for no hormones, or one or more of GH, PRL, βTSH, and/or α-subunit	Focal/variable
Acidophil stem cell tumor		PIT1, ERα	Monomorphic tumor cells with PRL (predominant) and GH (focal/variable)	Scattered fibrous bodies
Mixed somatotroph and lactotroph tumor*		PIT1, ERα**	Somatotroph tumor component: GH ± α-subunit depending on tumor subtype; lactotroph tumor component: PRL (diffuse or paranuclear depending on the subtype)	Tumor subtype characteristics
TPIT-lineage PitNETs				
Corticotroph tumors	Densely granulated corticotroph tumor	TPIT	ACTH and other POMC derivates	Strong, always diffuse
	Sparsely granulated corticotroph tumor			Variable (often diffuse)
	Crooke cell tumor			Perinuclear ring–like cytoplasmic
SF1-lineage PitNETs				
Gonadotroph tumor		SF1, ERα, GATA3	α-subunit, βFSH, βLH, or none	Variable or negative
PitNETs with no distinct cell lineage				
Plurihormonal tumor		Multiple combinations	Multiple combinations in a monomorphous tumor population	Variable
Null cell tumor		None	None	Variable

LMWK low molecular weight cytokeratin, *PitNET* pituitary neuroendocrine tumor

*These tumors are composed of two morphologically and immunohistochemically distinct tumor cell populations; **positive in the lactotroph tumor component

The subtypes of PitNETs are discussed within the framework of the normal cell counterparts, highlighting the features that are important in their diagnosis. Somatotroph, lactotroph, and corticotroph tumors are subtyped as sparsely and densely granulated; the densely granulated forms of somatotroph and corticotroph tumors resemble their normal counterparts and are usually highly hormonally active, whereas the sparsely granulated tumors are more aggressive, likely because they present at a later, more advanced stage due to less florid hormonal symptomatology. The reverse is true of lactotroph tumors that are far more commonly sparsely granulated, reflecting the normal status of

lactotrophs. An unusual and aggressive subtype of corticotroph PitNET is the Crooke cell tumor that illustrates the dichotomy of hormone feedback and growth control; these atypical lesions have Crooke's hyaline change suggesting feedback suppression of hormone synthesis and secretion, yet they are highly proliferative, aggressive tumors. Only thyrotroph and gonadotroph tumors have no recognized subtypes.

There are now also examples of PitNETs that are thought to represent tumors of precursor cells. These include the acidophil stem cell tumor and the immature PIT1-lineage tumor. These tumors are often (but not always) plurihormonal and do not show terminal differentiation based on morphology, immunoprofile, ultrastructure, and function. Importantly, the original description of the immature plurihormonal tumors used the nomenclature "poorly differentiated" to describe the cytology that was not characteristic of any differentiated PIT1-lineage cell [13]. However, in the context of the WHO/IARC common classification system for NENs, the term "poorly differentiated" is used for NECs, and these tumors are not nearly so undifferentiated; therefore, the term has been changed to "immature PIT1-lineage" to clarify this potential source of confusion. Another important addition is the mature plurihormonal PIT1-lineage tumor that resembles a mammosomatotroph tumor but also is responsible for secretion of TSH in addition to GH and PRL.

As in previous editions, the term "null cell" is used to describe PitNETs that have no evidence of adenohypophyseal lineage-specific differentiation based on complete lack of reactivity for not only pituitary hormones, but also PIT1, TPIT, SF1, and GATA3. As predicted at the time of their inception [14], these tumors are becoming much more rare with the use of more sophisticated tools to identify lineage determination.

There are very rare tumors that are composed of a single cell population that exhibits features of multiple adenohypophyseal lineages [15, 16]; these unusual plurihormonal PitNETs are accounted for as a separate type.

In previous editions, mixed tumors were recognized in the somatotroph category, but it is now evident that multiple synchronous PitNETs occur more often than previously thought [17]; this point has been highlighted by the use of transcription factor immunohistochemistry that allows the detection of discrete cells types in tumors that might otherwise be classified as "unusual plurihormonal" lesions.

Question 3: Which Ancillary Tools Are Required for the Assessment of Pituitary Neuroendocrine Tumors?

As is evident from the new WHO classification, there is an absolute need to identify tumor cell expression of transcription factors and hormones [12]. The role of IHC cannot be overemphasized. All PitNETs must be classified based on lineage, cell type, and hormone production as well as other ancillary features that allow characterization of subtypes (Table 1).

The approach to this need for extensive immunohistochemistry varies based on resource availability. In the ideal setting, all PitNETs should be stained for at least the three main transcription factors, PIT1, TPIT, and SF1 [1]; ideally, this panel should also include ERα and GATA3 [18]. Staining for hormones should include ACTH, GH, PRL, βTSH, βFSH, and βLH as well as the α-subunit of glycoprotein hormones (αSU), although some pathologists do not stain for βFSH and βLH given the high sensitivity of SF1 for detecting gonadotroph tumors [19]. The importance of keratins in determining cell type and tumor subtype must also be emphasized [20]; the most widely used antibody is the CAM5.2 clone but others including AE1/AE3 and CK18 are also satisfactory. As with other NETs, Ki67 is a part of the assessment but unlike other NETs, these tumors are not graded based on proliferation indices.

The ideal approach is to perform the complete panel of stains. However, in some places, this is not feasible; there is a proposal to use a tiered approach, starting with pituitary transcription factors [21, 22] followed by the relevant hormones applicable for the transcription factors identified. This approach is more cost-effective and can be used for small specimens that may not have sufficient tissue for a full workup [23, 24], but might miss unusual tumors that require more detailed evaluation [25].

Question 4: What Are the Pathological Correlates of Acromegaly?

It has long been recognized that acromegaly is not one disease [26] but rather is attributed to a group of neoplasms including rare ones outside the pituitary.

The commonest tumor associated with acromegaly is *the densely granulated somatotroph tumor* (Fig. 1) [19, 27]. This tumor is composed of densely granulated, strongly acidophilic cells that closely resemble nontumorous somatotrophs. They are usually highly hormonally active, and the patients present with florid disfigurement that is readily appreciated on cursory examination. The tumor cells express PIT1, GH, and αSU and have a characteristic perinuclear pattern of keratin staining. Because of their hormonal activity, they are usually diagnosed at a younger age and when smaller than their related sparsely granulated subtype that may go undetected until they create symptoms of a mass and are, therefore, often extrasellar at diagnosis.

The *sparsely granulated somatotroph tumor* (Fig. 2) is composed of chromophobic cells that have few secretory granules and may be negative or only focally weakly positive for GH, but they have a characteristic cytoplasmic globule that can be seen on H&E staining and is decorated by stains for keratins such as CAM5.2, CK18, and AE1/AE3 [20]. In addition to this

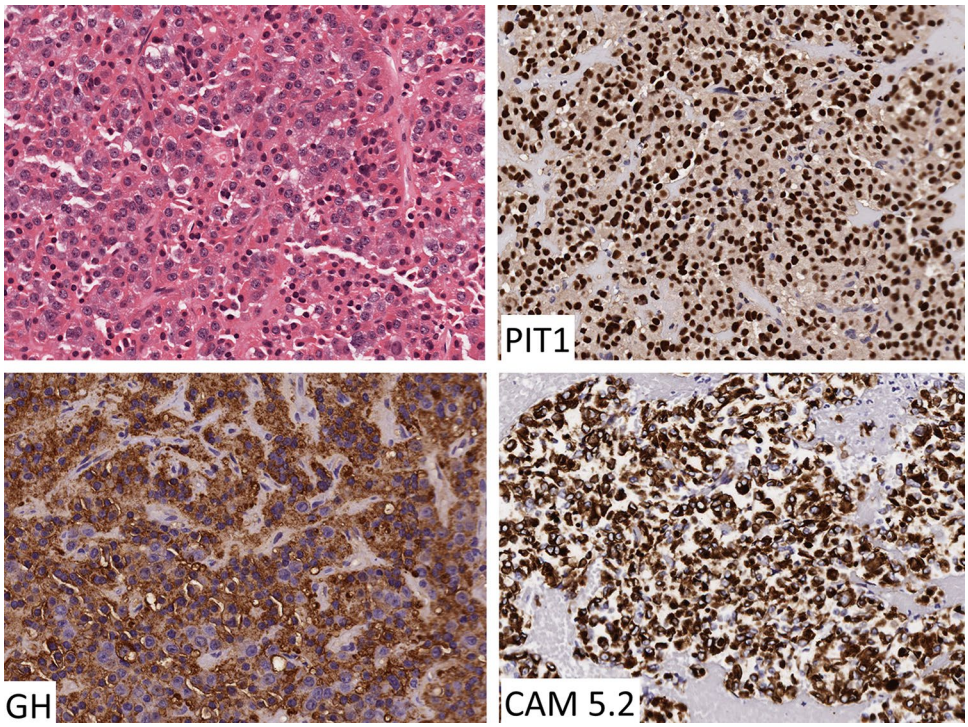

Fig. 1 Densely granulated somatotroph tumor. These tumors are composed of large cells with acidophilic cytoplasm, nuclear positivity for PIT1, diffuse strong cytoplasmic reactivity for GH, and intense perinuclear keratins using the CAM 5.2 stain

keratin pattern, they express PIT1 diffusely but they are usually negative for αSU and all other pituitary transcription factors and hormones. The fibrous body is present in the vast majority of tumor cells and is the hallmark of this PitNET.

Densely granulated somatotroph tumors are highly enriched for tumors with *GNAS* activating mutations [28] and the high cAMP levels that are characteristic of this tumor account for the consistent expression of αSU and explain the sensitivity of these tumors to somatostatin inhibition, whereas the sparsely granulated subtype tends to be more resistant to this therapeutic approach [27]. These tumor subtypes can be distinguished preoperatively based on the clinical and biochemical features as well as their radiological features including the hyperintensity of sparsely granulated tumors on T2-weighted magnetic resonance imaging (MRI) [26, 27]. Occasional tumors have the predominant morphology of densely granulated tumors but contain scattered fibrous bodies associated with diffuse perinuclear keratin staining; these so-called "intermediate" forms are clinically, biochemically, radiologically, and prognostically indistinguishable from densely granulated tumors [29] and are therefore classified within that category.

Other PitNETs can also cause acromegaly. These include *mammosomatotroph tumors* (Fig. 3) that not only resemble densely granulated somatotroph tumors but also express ERα and PRL in many tumor cells and *mature plurihormonal PIT1-lineage tumors* (Fig. 4) that not only are similar but also express variable GATA3 and βTSH. These are both strongly acidophilic tumors that resemble nontumorous mammosomatotrophs and give rise to florid acromegaly that is associated with additional hormone hypersecretion including hyperprolactinemia that is greater than expected from hypothalamic interruption and, in the case of the plurihormonal tumor, hyperthyroidism.

In contrast, the immature PIT1-lineage tumor and the acidophil stem cell tumor represent less differentiated cells that do not resemble any terminally differentiated "mature" cells that are known to exist in the mature normal gland. Both of these immature tumor types have unusual keratin profiles that vary from diffuse to focal and they may have scattered fibrous bodies.

Immature PIT1-lineage tumors (Fig. 5) are composed of polygonal or even spindle-shaped chromophobic cells that more closely resemble thyrotrophs; these tumors may be clinically silent or may cause acromegaly, hyperprolactinemia, and/or central hyperthyroidism; they consistently stain for PIT1 but may have variable, usually only focal positivity for one or more than one PIT1-lineage hormones including GH, PRL (associated with ERα), and/or βTSH (associated with GATA3); and they tend to be relatively aggressive, with large unresectable tumors at presentation.

Acidophil stem cell tumors (Fig. 6) are also large tumors at presentation and are usually associated with hyperprolactinemia but less than expected for the size of the tumor; they may also give rise to a very subtle "fugitive acromegaly" [23]. Unlike in the 2017 WHO classification, the acidophil stem cell tumor is separated from the lactotroph tumor family and now stands out as a distinct PIT1-lineage tumor. These tumors have characteristic oncocytic cytology with massive dilated "giant" mitochondria that can be seen as

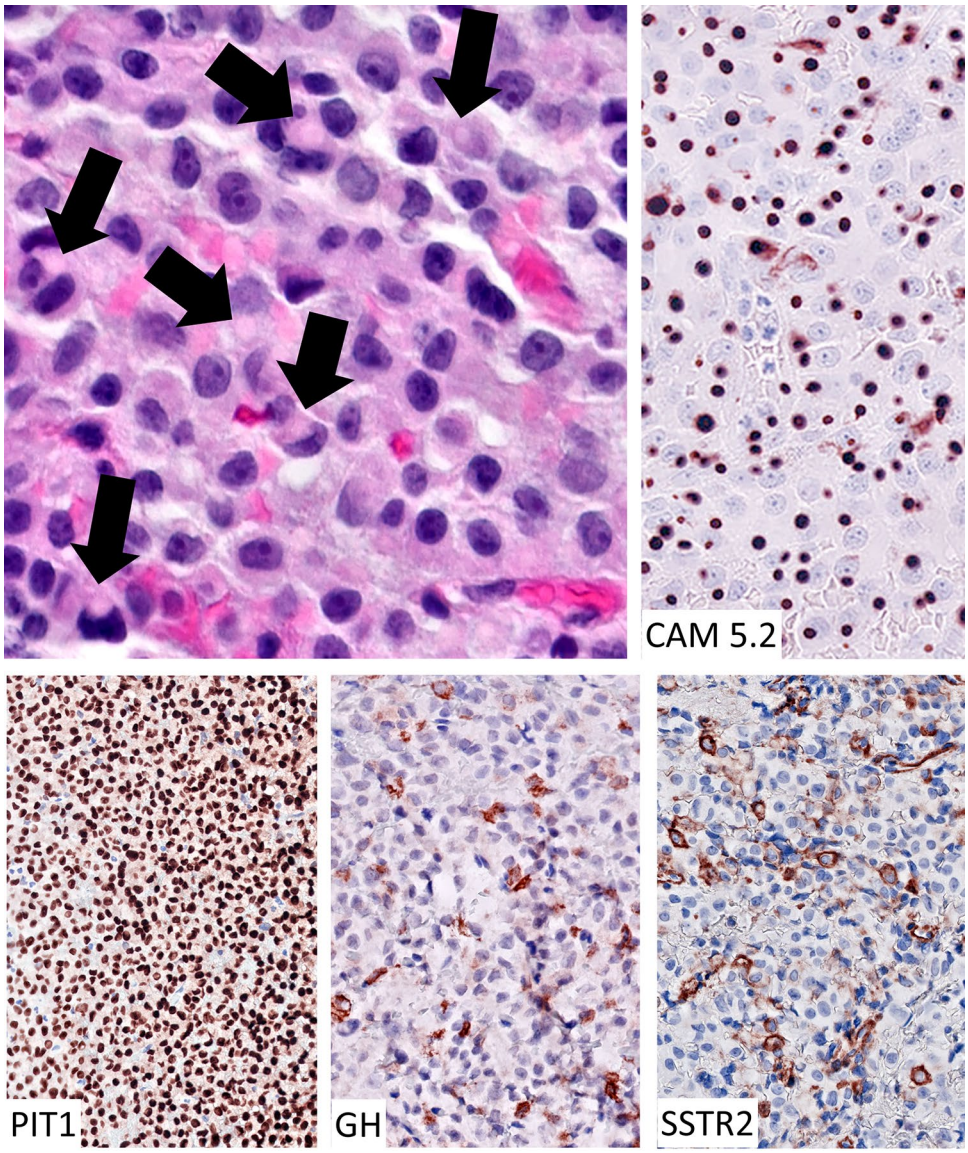

Fig. 2 Sparsely granulated somatotroph tumor. These tumors are composed of large cells with chromophobic cytoplasm that harbors pale round structures (arrows) that correspond to keratin aggresomes known as fibrous bodies. They have nuclear positivity for PIT1 but only scant variable cytoplasmic reactivity for GH and incomplete weak membranous staining for SSTR2

cytoplasmic vacuoles on H&E staining. They stain for PIT1 and ERα, have extensive PRL but only focal GH immunoreactivity, and generally do not express αSU.

The category of *mixed somatotroph-lactotroph tumors* is used to describe tumors that are composed of two distinct populations of tumor cells that can be recognized, usually on H&E but certainly on immunoprofiling. They are most often composed of densely granulated somatotrophs and sparsely granulated lactotrophs (see next section), but occasional tumors are composed of sparsely granulated somatotrophs and sparsely granulated lactotrophs.

Acromegaly can rarely be caused by eutopic or ectopic production of GH-releasing hormone (GHRH) [10, 11, 30, 31] and even less commonly by ectopic GH [32]. Eutopic disease takes the form of either a gangliocytoma or a composite tumor composed of gangliocytoma with a somatotroph tumor, usually a sparsely granulated somatotroph tumor. Ectopic GH results in no pituitary enlargement, so the gland is not usually biopsied, but ectopic GHRH can be missed and considered to be primary pituitary disease because of the resulting somatotroph hyperplasia. Pituitary hyperplasia should be considered when the imaging identifies uniform sellar enlargement with no distinction between a non-enhancing neoplasm and an enhancing normal rim, but this is occasionally overlooked and the pathologist is responsible for making the diagnosis of hyperplasia. The importance of reticulin or collagen IV staining is emphasized for this distinction [1] that will lead to a workup for the primary source of disease that can be in the lung, pancreas, adrenal, or other sites.

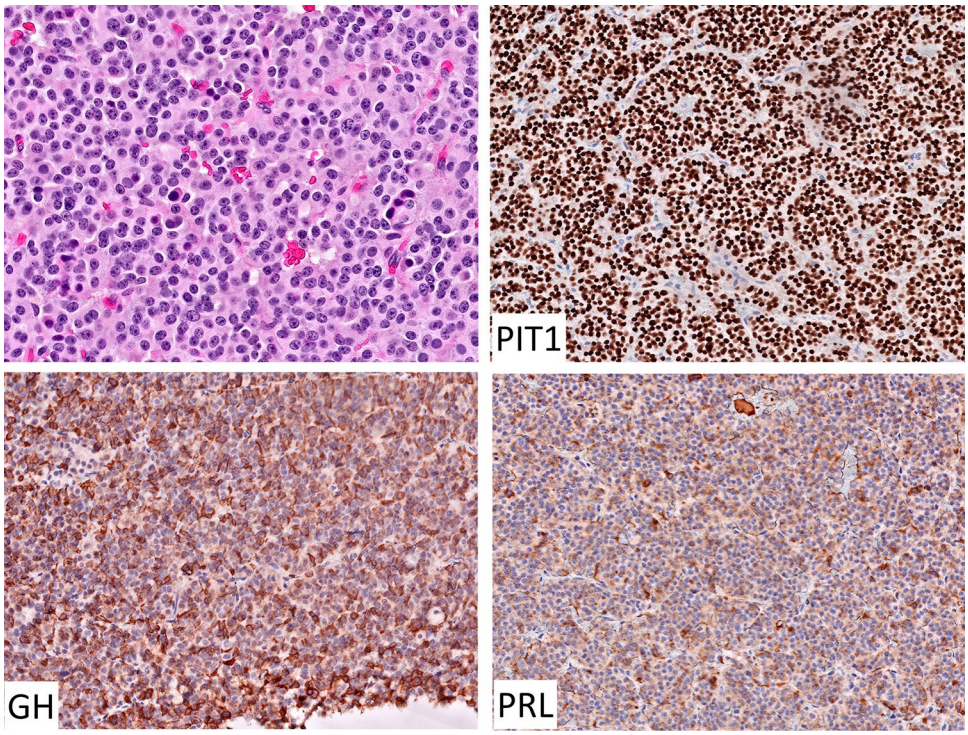

Fig. 3 Mammosomatotroph tumor. Like densely granulated somatotroph tumors, these tumors are composed of large cells with acidophilic cytoplasm, nuclear positivity for PIT1, diffuse strong cytoplasmic reactivity for GH, and intense perinuclear keratins (not shown), but they also express ER (not shown) and PRL

Question 5: What Are the Pathological Correlates of Hyperprolactinemia?

Hyperprolactinemia is a feature of almost any mass lesion in the sella that interferes with the transmission of dopamine to the adenohypophysis; this so-called "stalk section effect" is responsible for moderate elevations in circulating PRL that is regulated by tonic inhibition from the hypothalamus. This can be seen with any PitNET that does not synthesize or secrete prolactin, with tumors in the sella that do not completely destroy the adenohypophysis (such craniopharyngiomas, meningiomas, and soft tissue tumors) as well as with inflammatory conditions that cause sellar enlargement, the various forms of hypophysitis [1]. Hyperprolactinemia due to a prolactin-secreting PitNET comes in many flavors. The term “prolactinoma” is meaningless for histopathological tumor classification.

The vast majority of these tumors are pure lactotroph tumors that comprise almost half of cases in almost every epidemiologic series [6, 33] but not in surgical series [19]. These are *sparsely granulated lactotroph tumors* (Fig. 7) that usually respond exquisitely to dopamine agonist therapy with normalization of hormone levels and tumor shrinkage. One of the clues to this diagnosis is the exceptional correlation between tumor size and prolactin level. Sparsely granulated lactotroph tumors are composed of chromophobic tumor cells that express PIT1, ERα, and PRL; the PRL staining has a highly characteristic juxtanuclear dot-like staining pattern that corresponds to the Golgi complex. These tumors are negative for GH, αSU, βTSH, and other pituitary transcription factors including GATA3. CAM5.2 expression is often variable. Interestingly, these tumors tend to be indolent in women but are more aggressive in men [34].

A very rare lactotroph tumor subtype is the *densely granulated lactotroph tumor* (Fig. 8) that tends to present as a very large mass with very high prolactin levels that can be resistant to dopamine agonist therapy. These tumors are distinguished from their sparsely granulated counterparts by the presence of diffuse cytoplasmic PRL expression.

Other PIT1-lineage PitNETs can synthesize and secrete PRL, sometimes with other hormones, but the correlation with tumor size is not nearly as clear. These include *mammosomatotroph tumors, mature plurihormonal PIT1-lineage tumors, mixed somatotroph-lactotroph tumors* (all three with acromegaly), *immature PIT1-lineage tumors* (that may also have unusual presentations including acromegaly and/or hyperthyroidism or may be clinically silent with hyperprolactinemia in the range of stalk effect), and the *acidophil stem cell tumor* that usually is unassociated with other hormone excess but may give rise to very subtle or “fugitive” acromegaly. Other rare mixed tumors may also have a lactotroph component that would not cause hyperprolactinemia proportional to tumor size because the other components alter the tumor size without being responsible for PRL secretion.

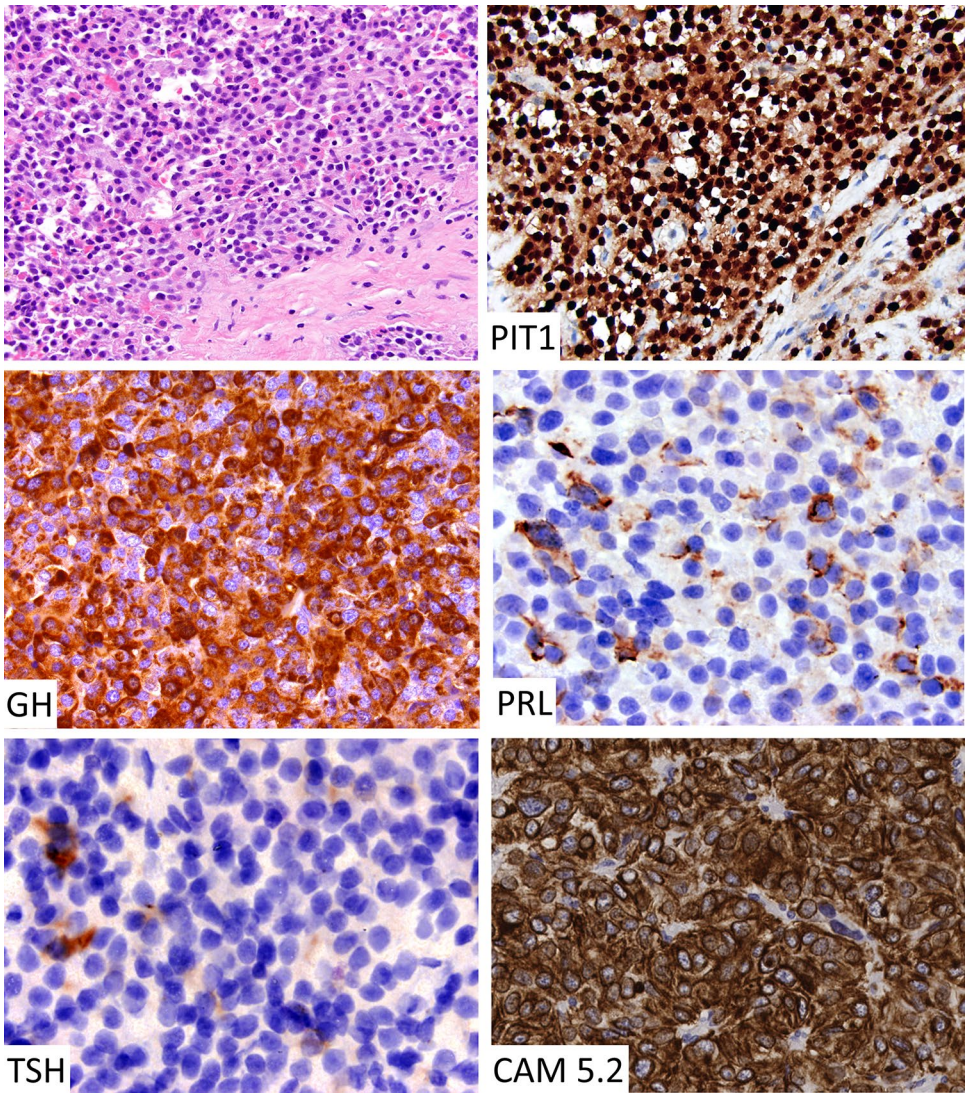

Fig. 4 Mature PIT1-lineage tumor. Like mammosomatotroph tumors, these tumors are composed of large cells with acidophilic cytoplasm, nuclear positivity for PIT1, diffuse strong cytoplasmic reactivity for GH, variable positivity for ER (not shown) and PRL, and intense perinuclear keratins (CAM 5.2), but they also express TSH and GATA3 (not shown)

Question 6: What Are the Pathological Correlates of TSH Excess?

One of the most important changes in the new classification is the emphasis on the various types of PitNETs that can secrete TSH. These include *thyrotroph tumors* (Fig. 9), *immature PIT1-lineage PitNETs*, *mature plurihormonal PIT1-lineage PitNETs*, any of these tumors in the context of *multiple synchronous PitNETs*, and *unusual plurihormonal PitNETs.*

Much of the literature is filled with case reports and series of "TSHomas" a term that may be clinically relevant but is meaningless as a biological tumor classification [35]. These series include pure thyrotroph tumors as well as mature plurihormonal PIT1-lineage tumors that often cause acromegaly and hyperthyroidism [23, 24] and immature PIT1-lineage tumors that may have unusual presentations including hyperthyroidism [13] but may also be clinically silent with hyperprolactinemia in the range of stalk effect. TSH-producing tumors have been traditionally considered to be aggressive with extensive fibrosis and invasive behavior that precludes gross total surgical resection; however, the inclusion of immature PIT1-lineage tumors that have those specific features of aggressive behavior is likely responsible for this fallacy, as most mature thyrotroph tumors may be fibrotic but are not really highly invasive.

An important differential diagnosis that is often seen clinically is thyrotroph hyperplasia due to primary thyroid failure with hypothyroidism. This results from an incomplete biochemical assessment and poor radiology interpretation that fails to recognize complete sellar enlargement with no enhancing rim of normal tissue that is seen as a feature of PitNETs [1]. In this situation, the pathologist should recognize the expanded but intact reticulin framework as well as the presence of intermixed nontumorous cells of all types. This is one rationale for the proposal to perform reticulin or collagen IV stains as a matter of routine and to perform the complete battery of immunostains for all pituitary transcription factors and hormones.

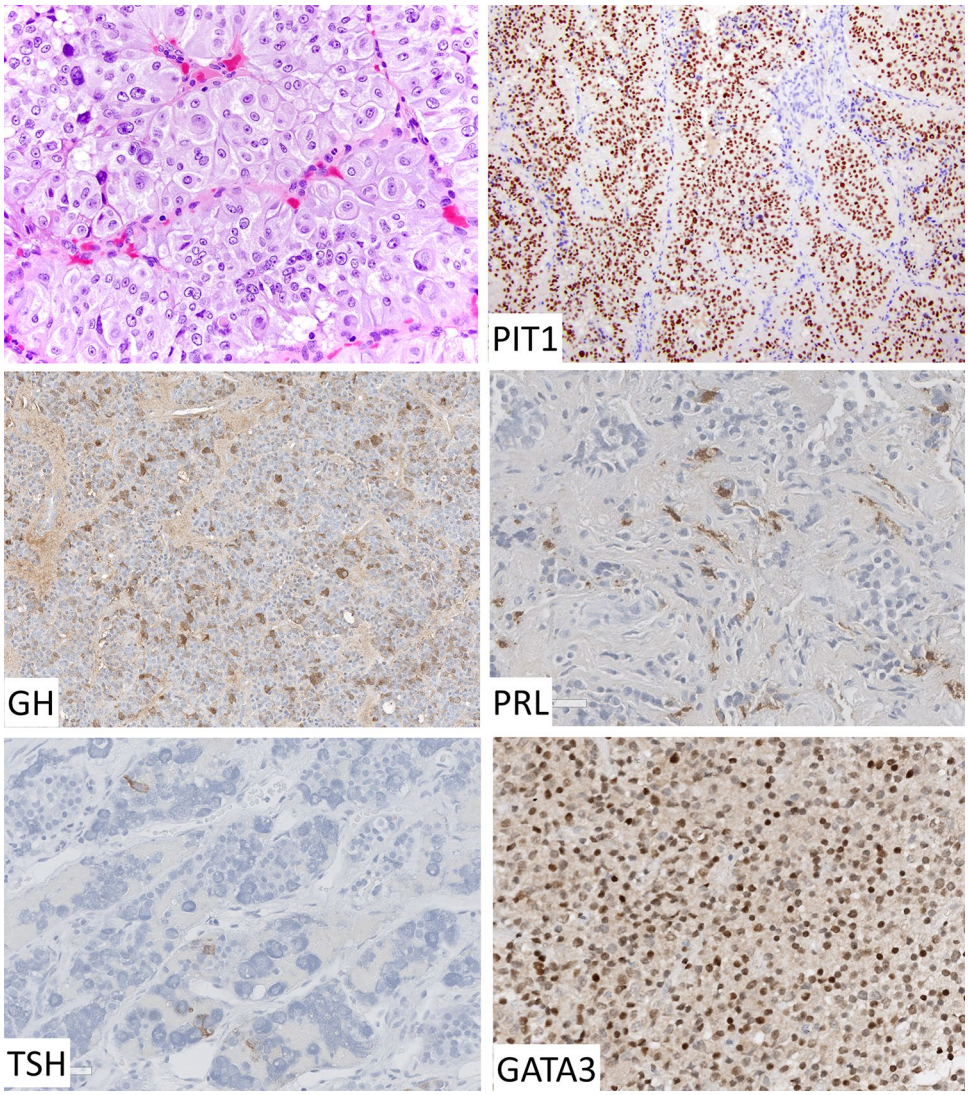

Fig. 5 Immature PIT1-lineage tumor. These unusual tumors are composed of spindle and epithelioid cells with nuclear pleomorphism and prominent nuclear inclusions known as spheridia. The only consistent immunohistochemical finding is diffuse nuclear PIT1 positivity. They can have variable GH, PRL, and/or TSH in any combination, with ER (not shown) and GATA3 expression correlating with PRL and TSH, respectively

Question 7: What Are the Pathological Correlates of Cushing Disease?

The clinical diagnosis of Cushing disease varies from a florid disorder that can be diagnosed at first glance to one of the most challenging scenarios in which multiple complex tests are required. As with acromegaly, there are subtypes of corticotroph tumors that are associated with distinct clinical features and have different prognosis and responses to therapy [1, 36]. As in the 2017 WHO classification, corticotroph tumors are classified based on the extent and distribution of their secretory granules as well as distribution of their cytoplasmic keratin filaments into three subtypes: (i) *densely granulated corticotroph tumor*, (ii) *sparsely granulated corticotroph tumor*, and (iii) *Crooke cell tumor.*

Densely granulated corticotroph tumors (Fig. 10) tend to be very small and associated with florid clinical manifestations of cortisol excess. These are characteristic basophilic and strongly PAS-positive tumors with nuclear TPIT, cytoplasmic ACTH, and very intense keratin reactivity. The biggest challenge with these tumors is due to their small size; they may not be visible on MRI, resulting in the need for inferior petrosal vein sampling to localize them; they may be missed because of a larger incidental "decoy" lesion [37]. Often the surgeon will try to identify them by filleting the gland in situ, and they may be lost to suction used to clear the hemorrhagic operative field; it is therefore recommended that the suction apparatus have a trap to catch all tissue. Despite this precaution, occasional patients will not have a detectable tumor yet they are cured by surgery; the diagnosis is supported by the presence of Crooke's hyaline change in the nontumorous gland that is both diagnostic of cortisol excess, excluding the differential diagnosis of a pseudo-Cushing disorder, and predictive of better outcome [38].

Sparsely granulated corticotroph tumors (Fig. 11) are usually larger and associated with less obvious Cushingoid

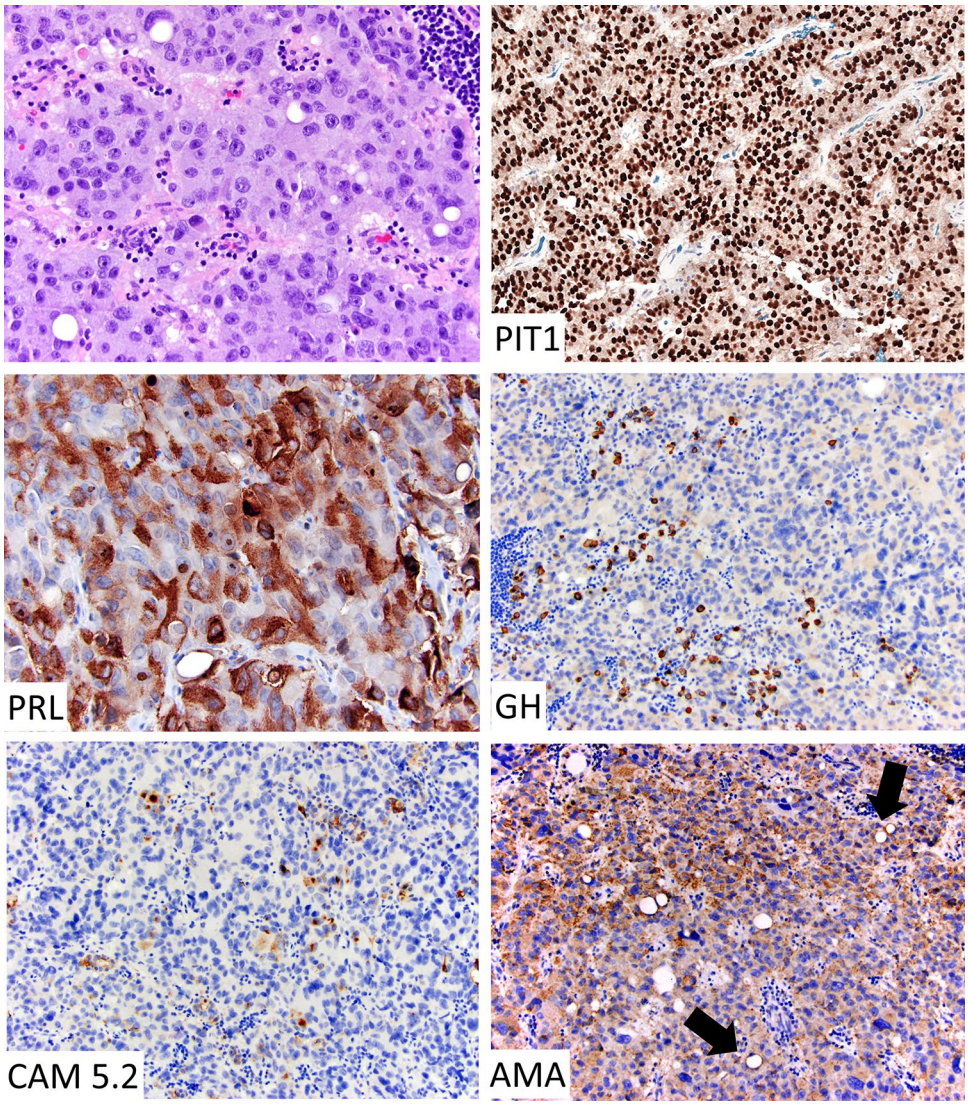

Fig. 6 Acidophil stem cell tumor. These are oncocytic tumors whose cells can have large dilated mitochondria that are visible as cytoplasmic vacuoles on routine microscopy. They consistently express nuclear PIT1 and ER (not shown) and cytoplasmic PRL, but they often have scant variable GH as well as focal fibrous bodies with CAM 5.2. The antimitochondrial antibody (AMA) yields strong positivity that highlights the dilated forms

features. There is some confusion in the literature about these lesions that have been classified as "silent" by some when they have no obvious clinical features but there is biochemical evidence of cortisol excess; a purist definition requires no evidence of cortisol excess for the diagnosis of a silent tumor. These tumors can be described as "whispering"; the accuracy of diagnosis is dependent on the degree of acuity of the clinician. These tumors are composed of chromophobic cells that have strong nuclear TPIT staining, variable, often focal and weak PAS and ACTH positivity, and intense cytoplasmic keratin reactivity. They too are associated with Crooke's hyaline change of nontumorous corticotrophs when functional, but not when silent. The distinction of a functioning tumor from a true silent one can also be confirmed using the biomarker p27 that is usually lost in functioning tumors but shows intact nuclear staining in silent tumors [19].

Crooke cell tumor (Fig. 12) is a rare subtype of corticotroph tumor. It is composed of tumor cells with Crooke's hyaline change, providing evidence of hormonal feedback inhibition. Paradoxically, these tumors are among the most proliferative and aggressive, invasive, recurrent, and metastatic PitNETs. They are composed of large cells with basophilic, PAS-, and ACTH-positive granules sequestered at the cell periphery or immediately next to the nucleus, while the cytoplasm is filled with a ring of pale hyaline material that is intensely reactive for keratins using CAM5.2, AE1/AE3, or CK18 [20].

As with acromegaly, the cause of ACTH-dependent cortisol excess may be outside the pituitary, and while the most common situation is ectopic ACTH that has no pituitary enlargement, occasional patients have ectopic CRH that causes corticotroph hyperplasia; the radiologic features and reticulin changes are similar to those of somatotroph and

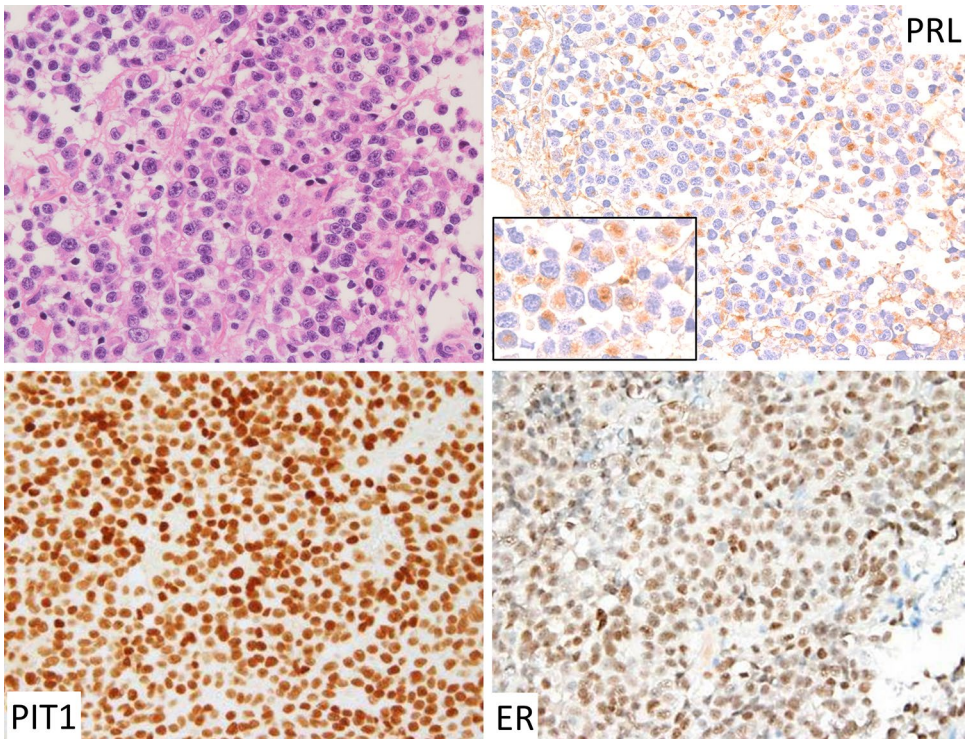

Fig. 7 Sparsely granulated lactotroph tumor. These tumors composed of cells with chromophobic cytoplasm have a highly characteristic pattern of juxtanuclear staining for PRL. They exhibit strong nuclear reactivity for PIT1 and ER

thyrotroph hyperplasia discussed above. Primary corticotroph hyperplasia as a cause of Cushing disease is a novel but rare disorder that can be very difficult to confirm, but is supported by the lack of Crooke's hyaline change in nontumorous corticotrophs [38].

Question 8: What Are the Pathological Correlates of Gonadotropin Excess?

Gonadotropin excess is exceptionally uncommon. While gonadotroph tumors (Fig. 13) are the most frequently resected PitNETs representing around 40% of these tumors [19], they are usually clinically silent. Rare functioning PitNETs are associated with elevated gonadotropins in the face of elevated gonadal steroids [39–41]. The most common scenario is that of a premenopausal woman with menstrual irregularity, infertility, polycystic ovaries, and even symptoms of ovarian hyperstimulation such as abdominal pain and bloating. Very rare cases of precocious puberty have been described. However, the majority of tumors associated with gonadotropin excess cause paradoxical hypogonadism. These tumors are not morphologically different from the far more common clinically silent gonadotroph tumors. The chromophobic cells can have solid or nesting architecture, but many have pseudopapillary growth and they may form characteristic pseudorosettes around vascular channels. It is important to distinguish these tumors that are often negative for hormones from metastatic NETs from non-pituitary primary sites, emphasizing the importance of transcription factor immunohistochemistry.

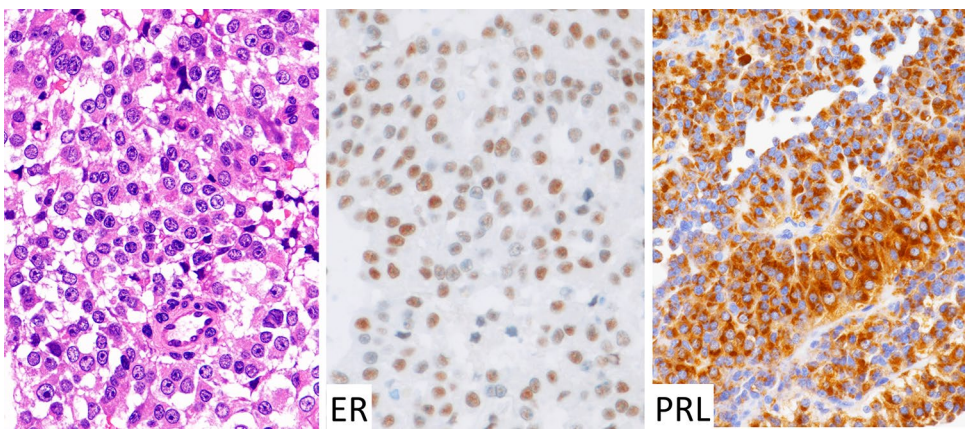

Fig. 8 Densely granulated lactotroph tumor. These very rare tumors are composed of loosely cohesive cells with pale chromophobic to acidophilic cytoplasm; they express nuclear PIT1 (not shown) and ER and diffuse cytoplasmic PRL

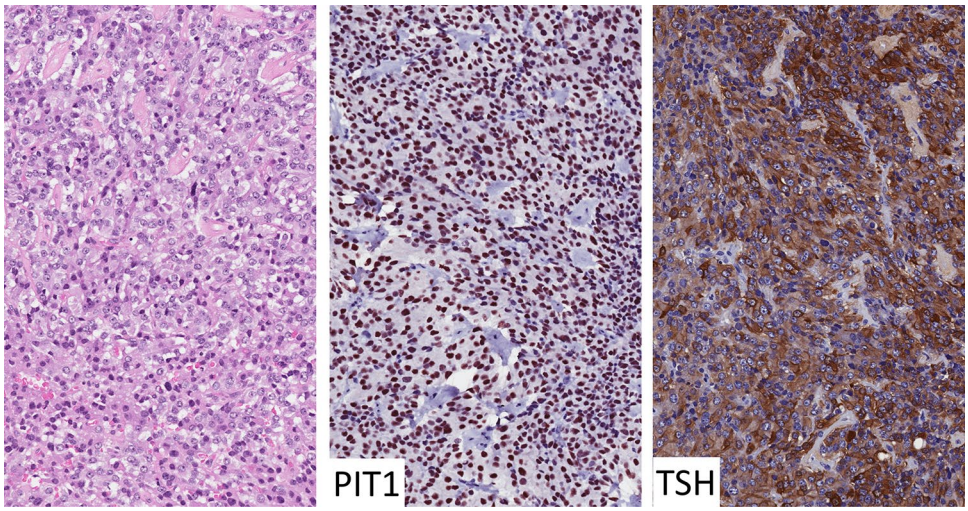

Fig. 9 Thyrotroph tumor. The typical thyrotroph tumor is composed of spindle shaped cells that stain for nuclear PIT1 and cytoplasmic TSH

These tumors stain for SF1, GATA3, and ERα, while staining for βFSH, βLH, and αSU is variable. Around 40% of these tumors lack keratin expression [19, 20], a finding that should not be mistaken for a sellar paraganglioma given their common GATA3 expression.

Question 9: What Is the Classification of Clinically Nonfunctioning PitNETs and Does It Matter?

The clinical term "non-functioning" is not a diagnosis but rather a description of a clinical scenario that has many differential diagnoses. These are tumors that are either incidental findings or present with symptoms of a sellar mass including headache, visual field defects, and hypopituitarism. The most common lesion is a gonadotroph tumor as described above; they constitute about 70–75% of clinically non-functioning PitNETs [19, 42]. In adults, the second most common clinically silent PitNETs are silent corticotroph tumors that can be densely or sparsely granulated and can be distinguished morphologically from functioning tumors only by the lack of Crooke's hyaline change in the surrounding nontumorous tissue and the presence of intact nuclear p27 [19]. In patients younger than 25 years, immature PIT1-lineage tumors are also common findings in patients with non-functioning PitNETs [43]. Occasional

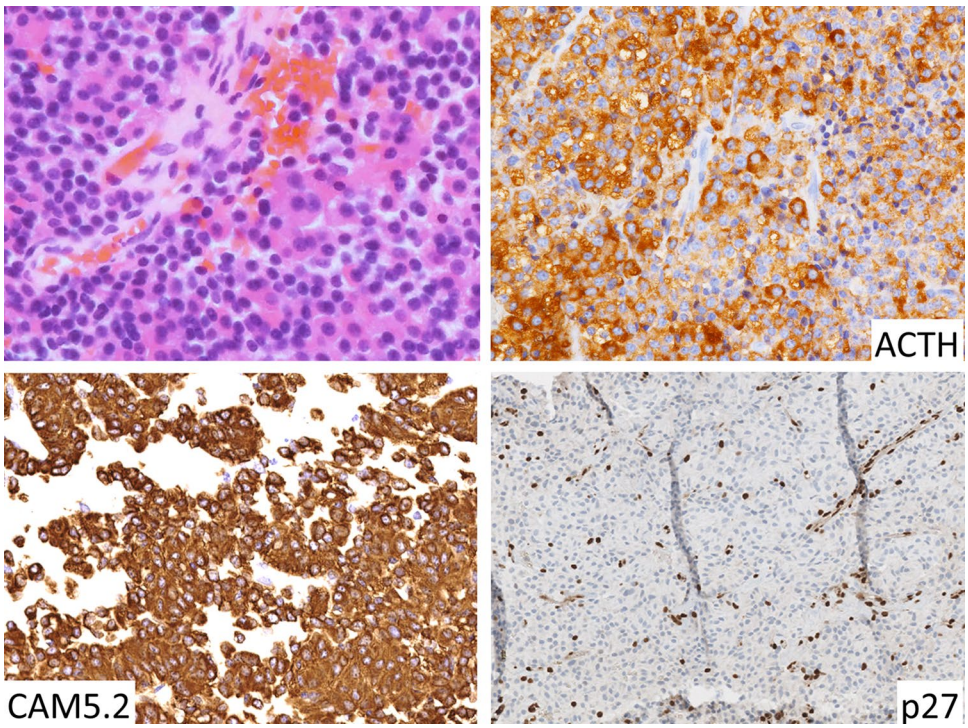

Fig. 10 Densely granulated corticotroph tumor. These classical basophilic tumors are composed of round tumor cells that have intense cytoplasmic ACTH and keratin (CAM 5.2) positivity and nuclear TPIT (not shown). When associated with Cushing disease, they are negative for p27 (with the normal endothelial and stromal cells serving as positive controls for the stain), a feature that is not seen in clinically silent tumors

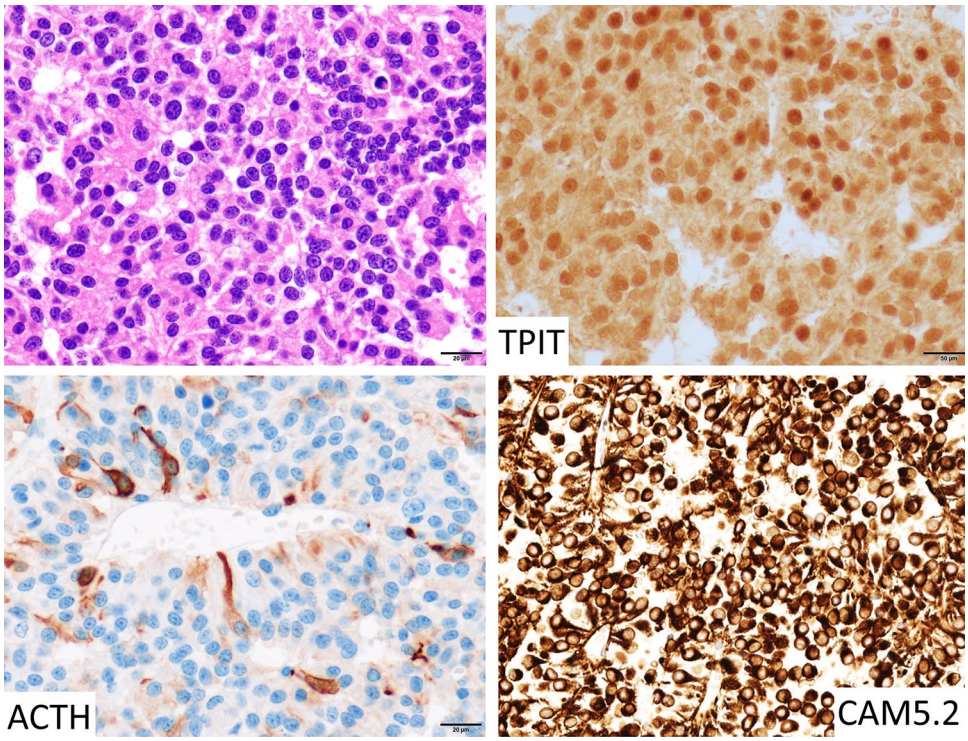

Fig. 11 Sparsely granulated corticotroph tumor. These tumors are composed of round tumor cells that have chromophobic cytoplasm with only variable ACTH but intense keratin (CAM 5.2) positivity and nuclear TPIT (not shown). These tumors also are negative for p27 when clinically functional (see Fig. 10)

tumors with morphological features of a PitNET but no biomarkers of lineage determination are classified as null cell tumors; these are decreasing in incidence as the tools used to classify these tumors improve [42, 44]. Other tumors can also present this way; the differential diagnosis is very large and includes metastatic NETs that can be easily confused without the application of transcription factors and hormones that assist in determination of site of origin [6].

The importance of accurate diagnosis lies not only in the exclusion of metastatic disease, which can portend a dismal

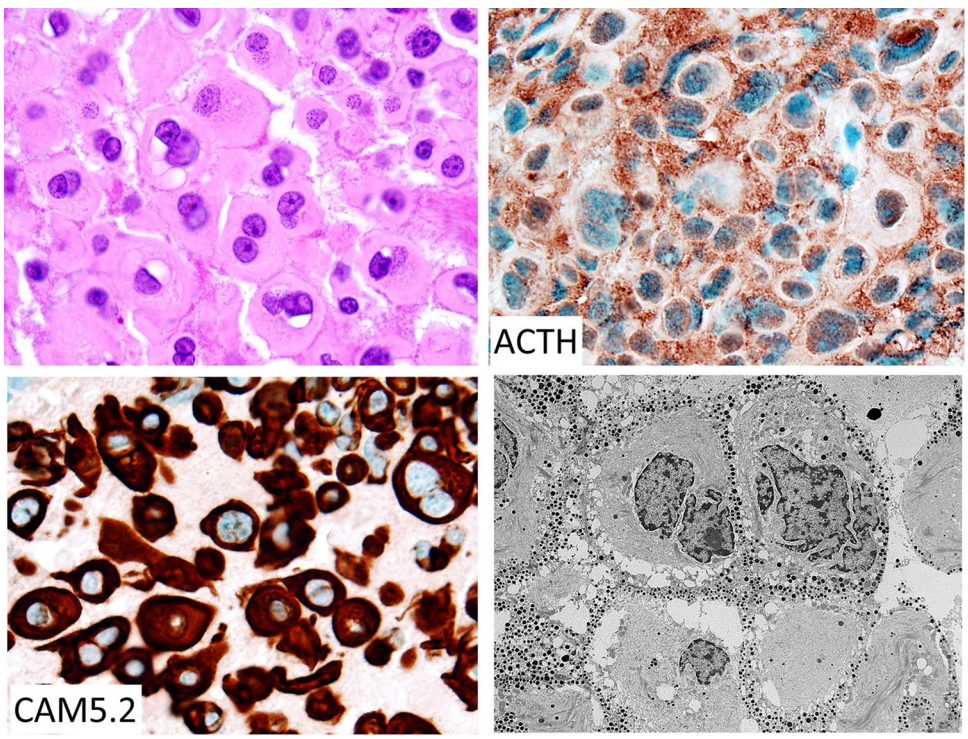

Fig. 12 Crooke cell tumor. These tumors are composed of corticotrophs that show evidence of glucocorticoid feedback suppression, the accumulation of pale pink hyaline cytoplasmic material that stains intensely for keratins (CAM 5.2), pushing the ACTH-immunoreactive cytoplasmic secretory granules to the cell periphery, or trapping it in a perinuclear location. Electron microscopy shows the concentric bundles of intermediate filaments that represent the keratin material

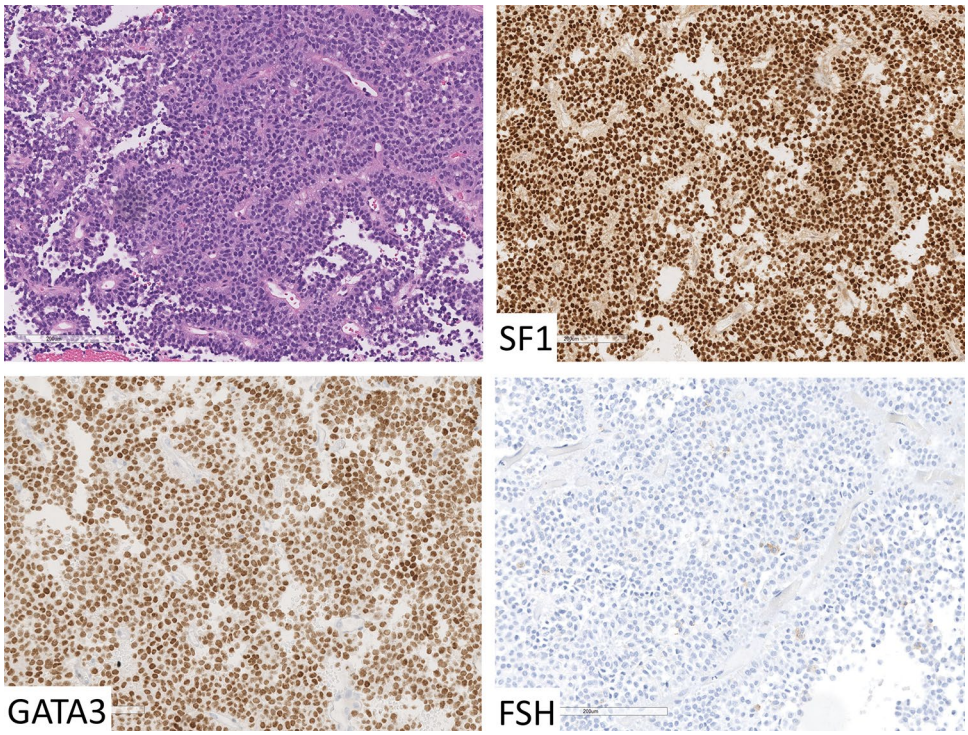

Fig. 13 Gonadotroph tumor. These tumors composed of chromophobic cells can form sheets, ribbons, trabecula, or rosettes around vascular channels. They have strong nuclear positivity for SF1 and GATA3 but hormone reactivity can be variable or absent; in this example there is only focal FSH staining

prognosis, but also in stratifying the prognosis of the PitNET, determining the needs for ancillary therapies such as external beam radiation, gamma knife radiosurgery, and peptide receptor radiotherapy. These treatments are not usually indicated for gonadotroph tumors but may be required for the more aggressive silent corticotroph tumors and immature PIT1-lineage tumors [6, 25, 28].

Question 10: How Can You Verify the Diagnosis of Multiple Synchronous PitNETs?

The incidence of multiple synchronous PitNETs has increased in the last 15 years due to the application of transcription factor immunohistochemistry [17, 45, 46]. The identification of a PitNET with multiple transcription factor profiles (Fig. 14) should prompt careful analysis of the distribution of the immunoreactivity that is usually accompanied by corresponding hormone positivity [12]. While there are exceptionally rare tumors that express transcription factors and hormones of multiple lineages in a single cell type [15, 16], it is far more common to have multiple synchronous neoplasms. These can only be diagnosed using a thorough immunohistochemical approach [12], and one must be careful to ensure that all cases are clinically diagnosed appropriately, and that research is performed on properly characterized samples [47].

Question 11: What Are the Relative Clinico-pathological Risks of the Various PitNET Tumor Types?

Unlike other NETs, PitNETs are not stratified into grades based on their Ki67 proliferation index; this is because there are far better biomarkers of aggressive behavior [48]. In fact, the classification of tumor type and subtype is of major clinical significance [49]. The stratification of tumors within each tumor lineage and cell type has been proven by clinical data as described in the sections above. For instance, among patients with acromegaly, it is recognized that sparsely granulated somatotroph tumors are more aggressive than densely granulated ones. Among patients with Cushing disease, sparsely granulated corticotroph tumors are more aggressive than densely granulated corticotroph tumors and Crooke cell tumors are exceptionally aggressive. Patients with pituitary tumor-dependent hyperthyroidism are stratified with immature PIT1-lineage tumors as the most aggressive cause. Among patients with hyperprolactinemia, the story is more complex with patient demographics playing a role in modifying tumor classification: while sparsely granulated lactotroph tumors tend to be very indolent and responsive to medical therapy, they can be aggressive in men, whereas the rare densely granulated subtype is generally always aggressive. Immature PIT1-lineage tumors tend to be aggressive irrespective of their clinical presentation,

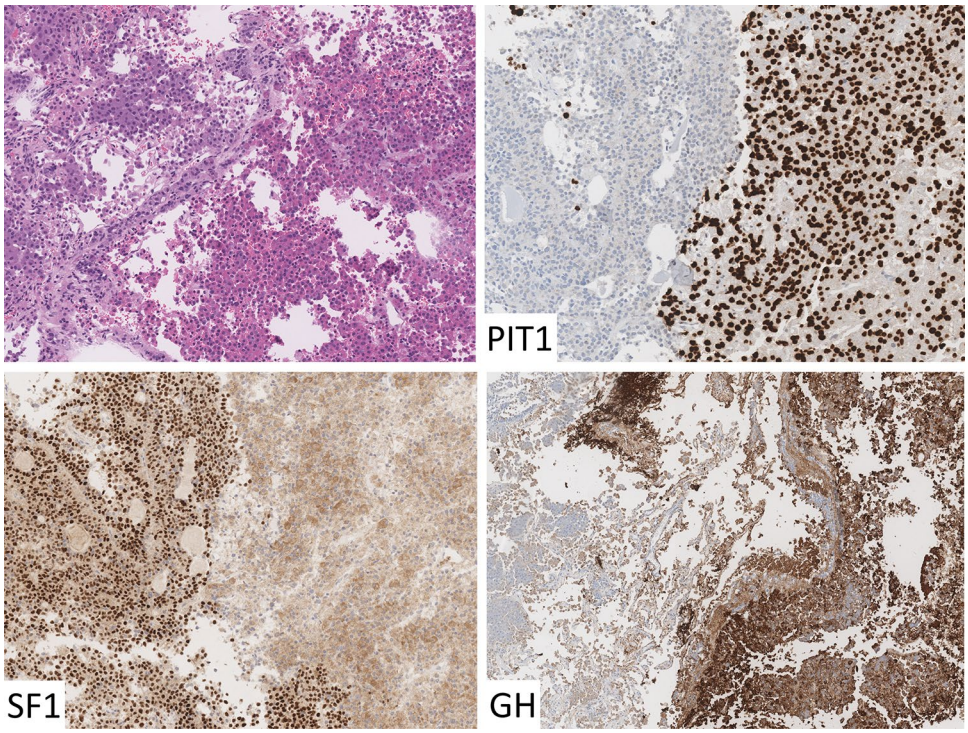

Fig. 14 Double PitNET. The coexistence of multiple PitNETs is not uncommon. Double tumors are most common, such as this one composed of a PIT1-lineage densely granulated somatotroph tumor on the right and a SF1-positive gonadotroph tumor on the left. Triple tumors may occur (not shown)

whether it be acromegaly, hyperthyroidism, hyperprolactinemia or as a clinically non-functioning tumor. Among clinically non-functioning tumors, silent corticotroph and silent PIT1-lineage tumors including the non-functional immature PIT1-lineage tumors are more aggressive than the more common silent gonadotroph tumors.

It should be noted that as yet, there is no staging system for PitNETs; however, the extent of tumor is a critical factor in determining prognosis. Microtumors that can be completely surgically resected have a much better prognosis than a tumor that extends into locations where it cannot be resected, such as the lateral cavernous sinus.

Question 12: What Is New in the Pathological Correlates of Pituitary Blastoma?

Pituitary blastoma (Fig. 15) is one of the hallmarks of DICER1 syndrome caused by pathogenic *DICER1* variants. This rare embryonal sellar tumor is composed of three distinct components including small undifferentiated/primitive blastemal cells, cuboidal/columnar Rathke's pouch epithelium with rosette or gland/follicle formation, and adenohypophyseal neuroendocrine cells. Neuroendocrine cells tend to show predominant corticotroph cell differentiation; this likely reflects the fact that corticotrophs are the first cell type to differentiate in the fetal pituitary [50, 51]. This entity was initially restricted to infantile Cushing disease with onset prior to 2 years of age; however, recent reports document the occurrence of pituitary blastoma in young adults [52, 53]. Careful review of follow-up data underscores that treatment-related complications rather than disease progression were the source of most deaths in affected patients [53, 54].

Question 13: What Is the Rationale for Consolidating Posterior Lobe Tumors?

Tumors arising in the posterior lobe have now been consolidated in the new WHO classification. In the past, the existence of multiple tumors of uncertain histogenesis gave rise to a nomenclature that is nonspecific and confusing. Tumors classified as "spindle cell oncocytomas" were originally thought to be derived from folliculostellate (sustentacular) cells of the anterior lobe. Granular cell tumors were of unknown origin. Tumors with ependymal morphology were called sellar ependymomas without any evidence of ependymal cells in the normal pituitary. Only pituicytomas were thought to derive from the glial-like cells that comprise the posterior lobe. However, with the recognition that pituicytes normally have subtypes that can be oncocytic, granular, or resembling ependymal cells, and using TTF1 as a biomarker of origin in the medial basal hypothalamus/posterior pituitary, it was proposed several years ago that these unusual tumors are all subtypes of *pituicytoma* (Fig. 16) [55]. Studies of their genetics and epigenetic methylation profiles have

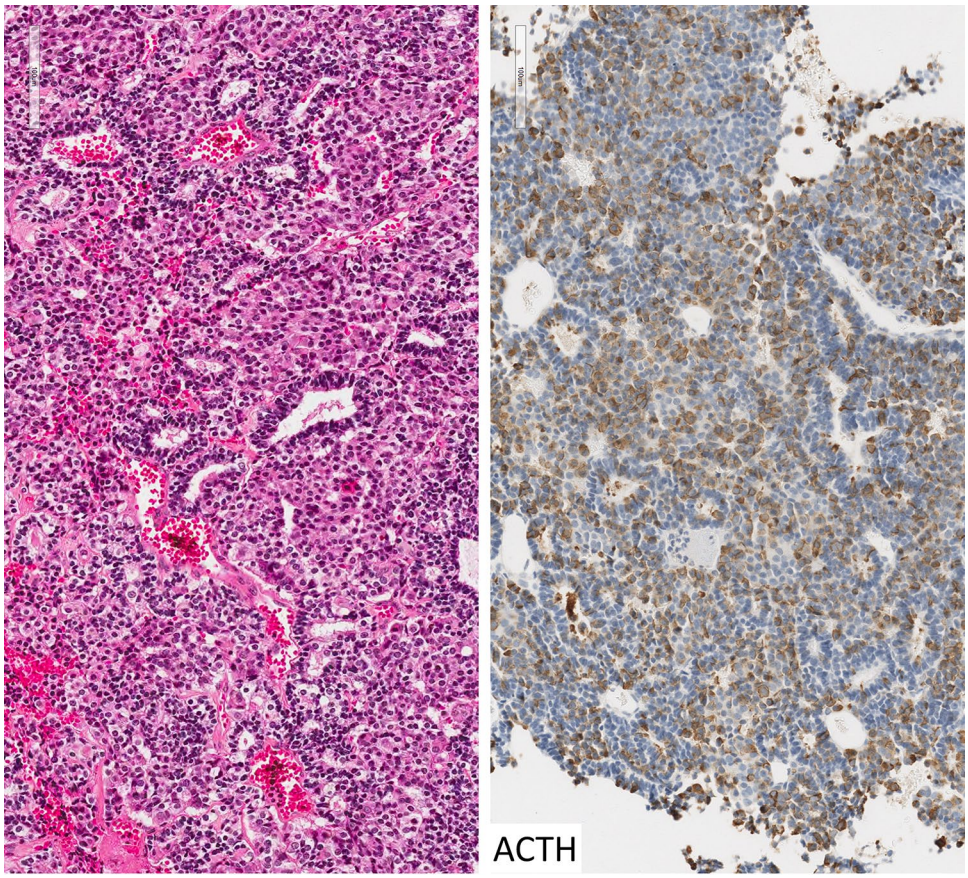

Fig. 15 Pituitary blastoma. This rare tumor is composed of small undifferentiated blastemal cells, cuboidal and columnar Rathke's pouch epithelium that can form rosettes, glands and follicles, and adenohypophyseal neuroendocrine cells that are most often positive for ACTH

supported this hypothesis and have expanded on prognostic subgroups in these tumors [56].

Question 14: What Is the Significance of the Sellar Neuronal Tumors?

One of the more exciting areas of this classification is the incorporation of hormone-producing neuronal tumors (Fig. 17). This area represents a true transition between neuronal and neuroendocrine neoplasia. The existence of ganglion cell tumors in this region has been recognized for many years, and some of these *gangliocytomas* have been associated with hypersecretion of hypothalamic (GHRH and CRH) and pituitary (GH, ACTH) hormones, resulting in acromegaly or Cushing disease, as well as occasional tumors causing other hormonal manifestations [57–59]. More recently, there have been reports of a number of tumors composed of small neurons, classified as *neurocytomas*, associated with vasopressin excess and the syndrome of inappropriate diuresis [60]. Interestingly, an intrasellar gangliocytoma producing small amounts of vasopressin caused Cushing disease, consistent with the known impact of vasopressin on corticotrophs [60]. These tumors expand the spectrum of neuroendocrine neoplasia to include TTF1-positive neuronal lesions.

Question 15: How Important Is the Pathologist in Identifying Germline Predisposition to Pituitary Tumors?

Pituitary tumors are a part of the spectrum of familial disorders known as the multiple endocrine neoplasia (MEN) syndromes [28]. PitNETs are a primary component of MEN1 (due to *MEN1* mutations), MEN4 (due to *CDKN1B* mutations), and the recently described MEN5 (due to *MAX* mutations), as well as manifestations of SDH deficiency syndromes (due to mutations in the SDH complex genes) and Carney complex (due to *PRKR1α* mutations); a patient with a germline pathogenic *CDC73* mutation also had an atypical MEN1-like syndrome with a PitNET. PitNETs are now being identified in patients with Lynch syndrome (due to deficiencies of *MLH1*, *MSH2*, *MSH6*, or *PMS2*); pituitary blastoma is pathognomonic of DICER1 syndrome.

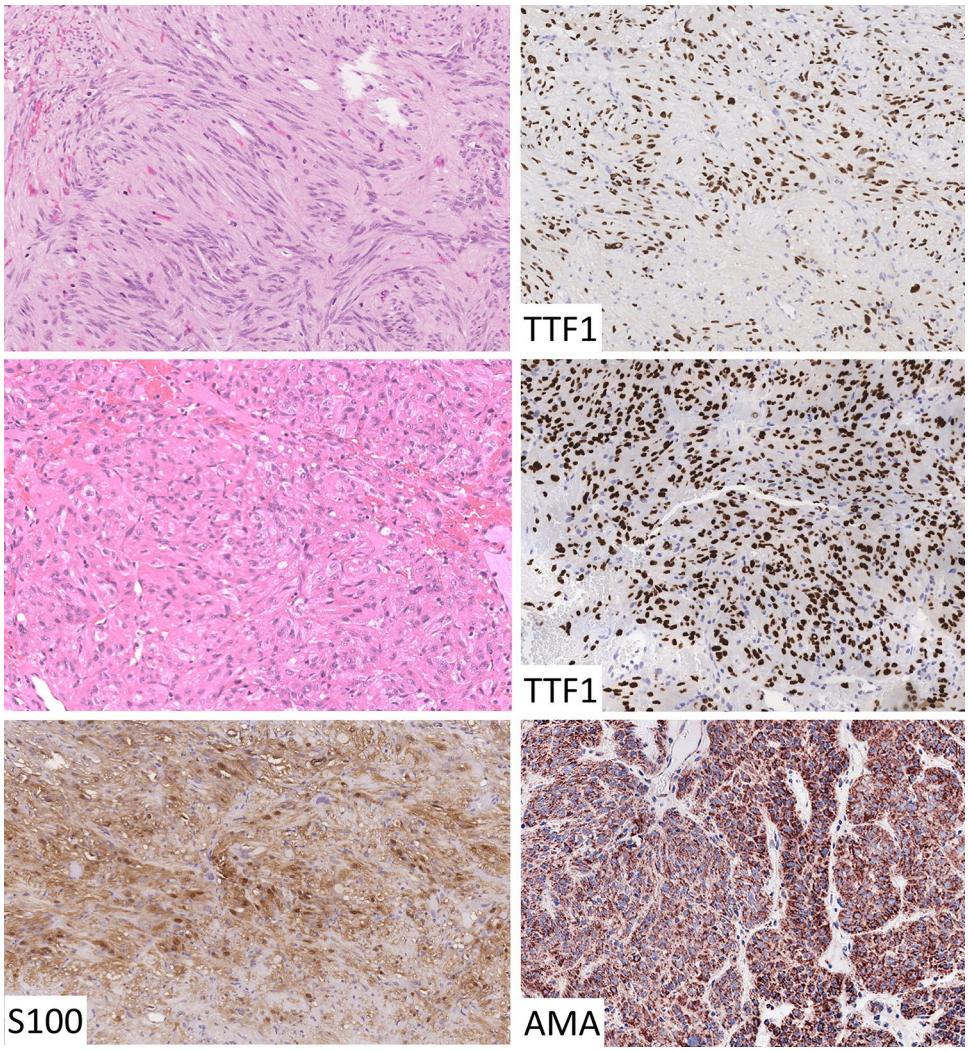

Fig. 16 Pituicytomas. Tumors that arise from pituicytes of the posterior lobe can have variable morphology, resembling spindle cell light and dark, oncocytic, granular, or ependymal pituicytes. The traditional pituicytoma is a spindle cell tumor (top row); the tumor formerly called spindle cell oncocytoma (middle and bottom rows) is now recognized to be an oncocytic subtype of pituicytoma. All pituicytomas feature nuclear TTF1 positivity and have variable S100 positivity. The oncocytic tumors have abundant AMA reactivity

Sporadic germline mutations in *GNAS* give rise to McCune-Albright syndrome with pituitary neoplasms as a main component. PitNETs occur as isolated tumors in families with the familial isolated pituitary adenoma (FIPA) syndrome due to *AIP* mutations and in children with X-linked acrogigantism (X-LAG). Some of these associations are characterized by specific tumor types. For example, patients with Carney complex, McCune-Albright syndrome, and X-LAG tend to have acromegaly due to mammosomatotroph tumors, whereas those with *AIP* mutations usually manifest sparsely granulated somatotroph tumors.

The only association that allows the morphologic tumor type to predict a genetic alteration is that of pituitary blastoma with DICER1 syndrome; however, while the vast majority of patients with pituitary tumors have sporadic disease, the pathologist can play an important role in identifying those who should be considered for genetic testing. Any young patient (under 30 years of age) with a pituitary tumor is a candidate for molecular testing, some of which can be approached with immunohistochemistry such as staining for menin in MEN1, p27 in MEN4, SDHB in SDH deficiency syndromes, parafibromin in HPTJT syndrome, and mismatch repair enzymes (MLH1, MSH2, MSH6, and PMS2) in Lynch syndrome. Loss of immunoreactivity for these tumor suppressor proteins with intact internal positive controls confirms a pathogenesis that should prompt germline testing. At this time, there is no high-quality staining for MAX protein that allows the detection of MEN5, but this is surely on the horizon. A young patient with acromegaly or gigantism and a sparsely granulated somatotroph tumor is at high suspicion for germline *AIP* mutation; however in this setting, loss of AIP immunoreactivity is not helpful, since most sporadic tumors of this type exhibit epigenetic downregulation of AIP [61]. Of course, any young child with early onset gigantism should be assessed for X-LAG. In any of the syndromic disorders, the association of a PitNET with another qualifying lesion should immediately prompt genetic evaluation with counselling for the patient and the family.

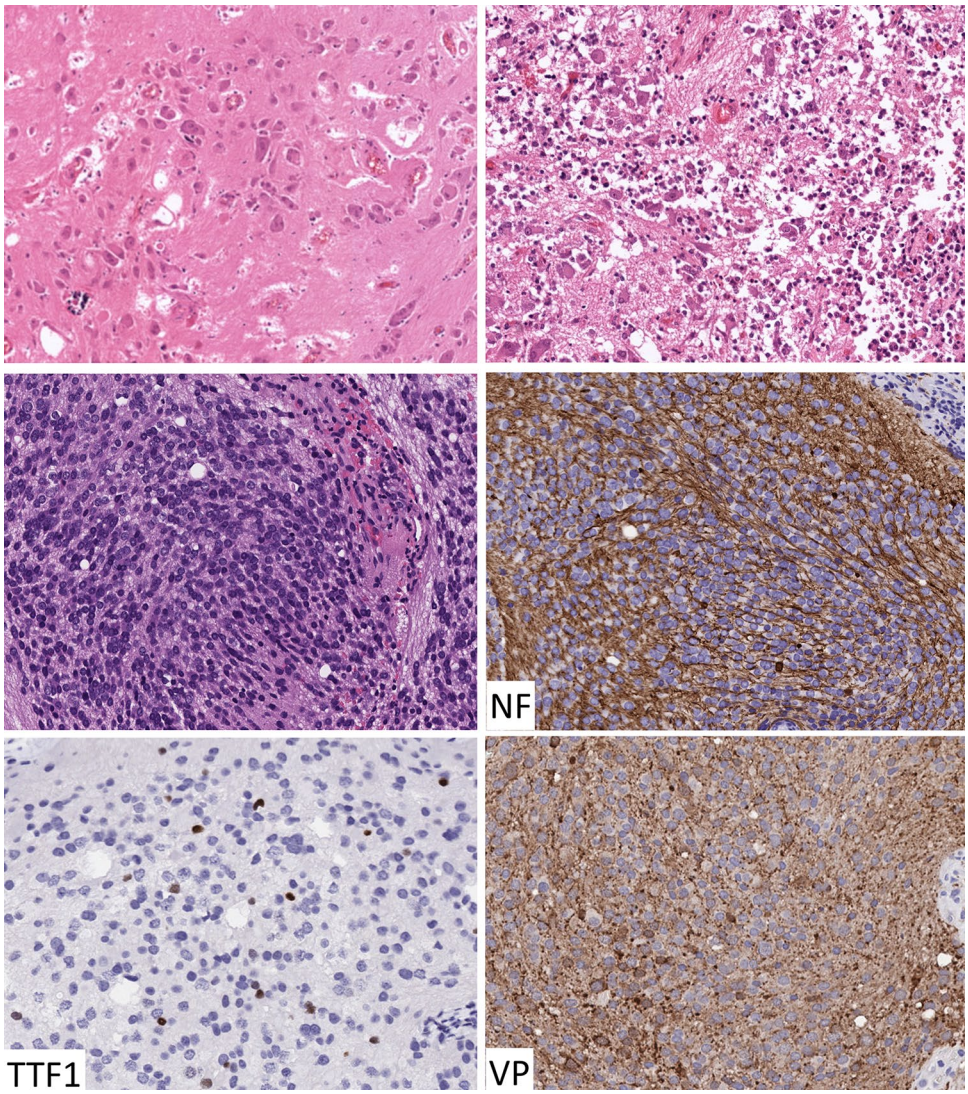

Fig. 17 Hypothalamic neuroendocrine tumors. Tumors composed of hypothalamic neurons occur in and around the sella turcica. Those composed of large mature ganglion cells are known as gangliocytomas; they may be pure neuronal neoplasms (top left) or admixed with a PitNET, most commonly a sparsely granulated somatotroph tumor (top right). Those composed of small neurons are known as neurocytoma (middle and bottom rows). These tumors can be identified by their strong expression of neurofilaments; they usually exhibit at least focal TTF1 nuclear reactivity, reflecting their origin from the ventral medial hypothalamus. These tumors may express hypothalamic hormones; vasopressin (VP) is the most frequent product of neurocytomas

Conclusion

The new WHO classification has incorporated tremendous advances in the understanding of the cytogenesis and pathogenesis of pituitary tumors of all types. While the advances in the field of craniopharyngiomas are not discussed here, the ability to classify these lesions based on immunohistochemistry for BRAF V600E mutant protein versus nuclear β-catenin expression has made correct diagnosis available to all pathologists with access to these tools [62] and in a subset, paves the way for targeted therapies [63]. Multiple chapters in the new classification discuss rare but important mesenchymal and stromal tumors, the unusual hematolymphoid lesions that occur in the sella, germ cell tumors that can mimic gonadotropin excess, and the metastases that occur in this region.

The major transformation to PitNETs raises the opportunity to implement structured reporting of these tumors [64, 65] and to consider the development of a staging system for pituitary tumors. As we continue to work on these aspects of pituitary pathology to improve patient care, we face the challenge of addressing the pathogenesis of the majority of these lesions that remain enigmatic despite so many years of study [28].

Author Contribution Conception and design: SLA, OM; data collection and analysis: SLA, OM, AP, RYO; manuscript preparation and editing: SLA, OM, AP, RYO; approval of final manuscript: SLA, OM, AP, RYO.

Declarations

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Consent for Publication All authors consent to publication.

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References

1. Asa, S. L. and Perry, A. (2020) Tumors of the Pituitary Gland. AFIP Atlas of Tumor and Non-Tumor Pathology, ARP Press, Arlington VA: ARP Press.
2. Osamura RY, Kajiya H, Takei M, Egashira N, Tobita M, Takekoshi S, Teramoto A (2008) Pathology of the human pituitary adenomas. Histochem Cell Biol 130: 495-507. https://doi.org/10.1007/s00418-008-0472-1
3. Vidal S, Horvath E, Kovacs K, Cohen SM, Lloyd RV, Scheithauer BW (2000) Transdifferentiation of somatotrophs to thyrotrophs in the pituitary of patients with protracted primary hypothyroidism. Virchows Arch 436: 43-51.
4. Horvath E, Lloyd RV, Kovacs K (1990) Propylthiouracyl-induced hypothyroidism results in reversible transdifferentiation of somatotrophs into thyroidectomy cells. A morphologic study of the rat pituitary including immunoelectron microscopy. Lab Invest 63: 511-520.
5. Jentoft ME, Osamura RY, Kovacs K, Lloyd RV, Scheithauer BW (2012) Transdifferentiation of pituitary thyrotrophs to lactothyrotrophs in primary hypothyroidism: case report. Virchows Arch 461: 221-225. https://doi.org/10.1007/s00428-012-1266-3
6. Asa S.L., Mete O, Cusimano MD, McCutcheon IE, Perry A et al. (2021) Pituitary Neuroendocrine Tumors: A Model for Neuroendocrine Tumor Classification. Mod Pathol. 34(9):1634-1650.
7. Asa SL, Casar-Borota O, Chanson P, Delgrange E, Earls P, Ezzat S, Grossman A, Ikeda H, Inoshita N, Karavitaki N, Korbonits M, Laws ER, Jr., Lopes MB, Maartens N, McCutcheon IE, Mete O, Nishioka H, Raverot G, Roncaroli F, Saeger W, Syro LV, Vasiljevic A, Villa C, Wierinckx A, Trouillas J (2017) From pituitary adenoma to pituitary neuroendocrine tumor (PitNET): an International Pituitary Pathology Club proposal. Endocr Relat Cancer 24: C5-C8. 24/4/C5 https://doi.org/10.1530/ERC-17-0004
8. Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, Busam KJ, de Krijger RR, Dietel M, El-Naggar AK, Fernandez-Cuesta L, Kloppel G, McCluggage WG, Moch H, Ohgaki H, Rakha EA, Reed NS, Rous BA, Sasano H, Scarpa A, Scoazec JY, Travis WD, Tallini G, Trouillas J, van Krieken JH, Cree IA (2018) 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 31: 1770-1786. https://doi.org/10.1038/s41379-018-0110-y
9. Williams MD, Asa SL, Fuller GN (2008) Medullary thyroid carcinoma metastatic to the pituitary gland: an unusual site of metastasis. Ann Diagn Pathol 12: 199-203.
10. Nasr C, Mason A, Mayberg M, Staugaitis SM, Asa SL (2006) Acromegaly and somatotroph hyperplasia with adenomatous transformation due to pituitary metastasis of a growth hormone-releasing hormone-secreting pulmonary endocrine carcinoma. J Clin Endocrinol Metab 91: 4776-4780.
11. Sanno N, Teramoto A, Osamura RY, Genka S, Katakami H, Jin L, Lloyd RV, Kovacs K (1997) A growth hormone-releasing hormone-producing pancreatic islet cell tumor metastasized to the pituitary is associated with pituitary somatotroph hyperplasia and acromegaly. J Clin Endocrinol Metab 82: 2731-2737. https://doi.org/10.1210/jcem.82.8.4175
12. Mete O, Asa SL (2020) Structure, Function, and Morphology in the Classification of Pituitary Neuroendocrine Tumors: the Importance of Routine Analysis of Pituitary Transcription Factors. Endocr Pathol 31: 330-336. https://doi.org/10.1007/s12022-020-09646-x
13. Mete O, Gomez-Hernandez K, Kucharczyk W, Ridout R, Zadeh G, Gentili F, Ezzat S, Asa SL (2016) Silent subtype 3 pituitary adenomas are not always silent and represent poorly differentiated monomorphous plurihormonal Pit-1 lineage adenomas. Mod Pathol 29: 131–142. https://doi.org/10.1038/modpathol.2015.151
14. Kovacs K, Horvath E, Ryan N, Ezrin C (1980) Null cell adenoma of the human pituitary. Virchows Arch [Pathol Anat] 387: 165-174.
15. Tordjman KM, Greenman Y, Ram Z, Hershkovitz D, Aizenstein O, Ariel O, Asa SL (2019) Plurihormonal Pituitary Tumor of Pit-1 and SF-1 Lineages, with Synchronous Collision Corticotroph Tumor: a Possible Stem Cell Phenomenon. Endocr Pathol 30: 74-80. https://doi.org/10.1007/s12022-018-9562-3
16. Tahara S, Kurotani R, Ishii Y, Sanno N, Teramoto A, Osamura RY (2002) A case of Cushing's disease caused by pituitary adenoma producing adrenocorticotropic hormone and growth hormone concomitantly: aberrant expression of transcription factors NeuroD1 and Pit-1 as a proposed mechanism. Mod Pathol 15: 1102-1105. https://doi.org/10.1097/01.MP.0000030451.28828.00
17. Mete O, Alshaikh OM, Cintosun A, Ezzat S, Asa SL (2018) Synchronous Multiple Pituitary Neuroendocrine Tumors of Different Cell Lineages. Endocr Pathol 29: 332-338. https://doi.org/10.1007/s12022-018-9545-4
18. Mete O, Kefeli M, Caliskan S, Asa SL (2019) GATA3 immunoreactivity expands the transcription factor profile of pituitary neuroendocrine tumors. Mod Pathol 32: 484-489. https://doi.org/10.1038/s41379-018-0167-7
19. Mete O, Cintosun A, Pressman I, Asa SL (2018) Epidemiology and biomarker profile of pituitary adenohypophysial tumors. Mod Pathol 31: 900-909. https://doi.org/10.1038/s41379-018-0016-8
20. Asa SL, Mete O (2021) Cytokeratin profiles in pituitary neuroendocrine tumors. Hum Pathol 107: 87–95. S0046–8177(20)30202–1 https://doi.org/10.1016/j.humpath.2020.10.004
21. McDonald WC, McDonald KN, Helmer JA, Ho B, Wang A, Banerji N (2021) The Role of T-box Transcription Factor in a Pituitary Adenoma Diagnostic Algorithm. Arch Pathol Lab Med 145: 592–598. 444337 https://doi.org/10.5858/arpa.2020-0091-OA
22. McDonald WC, Banerji N, McDonald KN, Ho B, Macias V, Kajdacsy-Balla A (2017) Steroidogenic Factor 1, Pit-1, and Adrenocorticotropic Hormone: A Rational Starting Place for the Immunohistochemical Characterization of Pituitary Adenoma. Arch Pathol Lab Med 141: 104-112. https://doi.org/10.5858/arpa.2016-0082-OA
23. Horvath E, Kovacs K, Smyth HS, Killinger DW, Scheithauer BW, Randall R, Laws ER, Jr., Singer W (1988) A novel type of pituitary adenoma: Morphological feature and clinical correlations. J Clin Endocrinol Metab 66: 1111-1118.
24. Manojlovic-Gacic E, Bollerslev J, Casar-Borota O (2020) Invited Review: Pathology of pituitary neuroendocrine tumours: present status, modern diagnostic approach, controversies and future perspectives from a neuropathological and clinical standpoint. Neuropathol Appl Neurobiol 46: 89-110. https://doi.org/10.1111/nan.12568
25. Asa SL (2021) Challenges in the Diagnosis of Pituitary Neuroendocrine Tumors. Endocr Pathol 32: 222-227. https://doi.org/10.1007/s12022-021-09678-x
26. Asa SL, Kucharczyk W, Ezzat S (2017) Pituitary acromegaly: not one disease. Endocr Relat Cancer 24: C1-C4. ERC-16–0496 https://doi.org/10.1530/ERC-16-0496
27. Asa SL, Ezzat S (2021) An Update on Pituitary Neuroendocrine Tumors Leading to Acromegaly and Gigantism. J Clin Med 10. https://doi.org/10.3390/jcm10112254
28. Asa SL, Mete O, Ezzat S (2021) Genomics and Epigenomics of Pituitary Tumors: What Do Pathologists Need to Know? Endocr Pathol 32: 3-16. https://doi.org/10.1007/s12022-021-09663-4

29. Obari A, Sano T, Ohyama K, Kudo E, Qian ZR, Yoneda A, Rayhan N, Mustafizur RM, Yamada S (2008) Clinicopathological features of growth hormone-producing pituitary adenomas: difference among various types defined by cytokeratin distribution pattern including a transitional form. Endocr Pathol 19: 82-91.
30. Sano T, Asa SL, Kovacs K (1988) Growth hormone-releasing hormone-producing tumors: clinical, biochemical, and morphological manifestations. Endocr Rev 9: 357-373.
31. Othman NH, Ezzat S, Kovacs K, Horvath E, Poulin E, Smyth HS, Asa SL (2001) Growth hormone-releasing hormone (GHRH) and GHRH receptor (GHRH-R) isoform expression in ectopic acromegaly. Clin Endocrinol (Oxf) 55: 135-140.
32. Ezzat S, Ezrin C, Yamashita S, Melmed S (1993) Recurrent acromegaly resulting from ectopic growth hormone gene expression by a metastatic pancreatic tumor. Cancer 71: 66-70.
33. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, McCutcheon IE (2004) The prevalence of pituitary adenomas: a systematic review. Cancer 101: 613-619.
34. Delgrange E, Trouillas J, Maiter D, Donckier J, Tourniaire J (1997) Sex-related difference in the growth of prolactinomas: a clinical and proliferation marker study. J Clin Endocrinol Metab 82: 2102-2107.
35. Luo P, Zhang L, Yang L, An Z, Tan H (2020) Progress in the Pathogenesis, Diagnosis, and Treatment of TSH-Secreting Pituitary Neuroendocrine Tumor. Front Endocrinol (Lausanne) 11: 580264. https://doi.org/10.3389/fendo.2020.580264
36. Rak B, Maksymowicz M, Pekul M, Zielinski G (2021) Clinical, Biological, Radiological Pathological and Immediate Post-Operative Remission of Sparsely and Densely Granulated Corticotroph Pituitary Tumors: A Retrospective Study of a Cohort of 277 Patients With Cushing's Disease. Front Endocrinol (Lausanne) 12: 672178. https://doi.org/10.3389/fendo.2021.672178
37. Booth GL, Redelmeier DA, Grosman H, Kovacs K, Smyth HS, Ezzat S (1998) Improved diagnostic accuracy of inferior petrosal sinus sampling over imaging for localizing pituitary pathology in patients with Cushing's disease. J Clin Endocrinol Metab 83: 2291-2295.
38. Akirov A, Larouche V, Shimon I, Asa SL, Mete O, Sawka AM, Gentili F, Ezzat S (2021) Significance of Crooke's Hyaline Change in Nontumorous Corticotrophs of Patients With Cushing Disease. Front Endocrinol (Lausanne) 12: 620005. https://doi.org/10.3389/fendo.2021.620005
39. Graillon T, Castinetti F, Chabert-Orsini V, Morange I, Cuny T, Albarel F, Brue T, Dufour H (2019) Functioning gonadotroph adenoma with severe ovarian hyperstimulation syndrome: A new emergency in pituitary adenoma surgery? Surgical considerations and literature review. Ann Endocrinol (Paris) 80: 122–127. S0003–4266(19)30025–3. https://doi.org/10.1016/j.ando.2018.11.007
40. Cote DJ, Smith TR, Sandler CN, Gupta T, Bale TA, Bi WL, Dunn IF, De GU, Woodmansee WW, Kaiser UB, Laws ER, Jr. (2016) Functional Gonadotroph Adenomas: Case Series and Report of Literature. Neurosurgery 79: 823-831. https://doi.org/10.1227/NEU.0000000000001188
41. Ntali G, Capatina C, Grossman A, Karavitaki N (2014) Clinical review: Functioning gonadotroph adenomas. J Clin Endocrinol Metab 99: 4423-4433. https://doi.org/10.1210/jc.2014-2362
42. Nishioka H, Inoshita N, Mete O, Asa SL, Hayashi K, Takeshita A, Fukuhara N, Yamaguchi-Okada M, Takeuchi Y, Yamada S (2015) The Complementary Role of Transcription Factors in the Accurate Diagnosis of Clinically Nonfunctioning Pituitary Adenomas. Endocr Pathol 26: 349-355. https://doi.org/10.1007/s12022-015-9398-z
43. Yamaguchi-Okada M, Inoshita N, Nishioka H, Fukuhara N, Yamada S (2012) Clinicopathological analysis of nonfunctioning pituitary adenomas in patients younger than 25 years of age. J Neurosurg Pediatr 9: 511-516. https://doi.org/10.3171/2012.1.PEDS11330
44. Lenders NF, Wilkinson AC, Wong SJ, Shein TT, Harvey RJ, Inder WJ, Earls PE, McCormack AI (2021) Transcription factor immunohistochemistry in the diagnosis of pituitary tumours. Eur J Endocrinol 184: 891-901. https://doi.org/10.1530/EJE-20-1273
45. Jastania RA, Alsaad KO, Al Shraim M, Kovacs K, Asa SL (2005) Double Adenomas of the Pituitary: Transcription Factors Pit-1, T-pit, and SF-1 Identify Cytogenesis and Differentiation. Endocr Pathol 16: 187-194.
46. Roberts S, Borges MT, Lillehei KO, Kleinschmidt-DeMasters BK (2016) Double separate versus contiguous pituitary adenomas: MRI features and endocrinological follow up. Pituitary 19: 472-481. https://doi.org/10.1007/s11102-016-0727-0
47. Mete O, Ezzat S, Perry A, Yamada S, Uccella S, Grossman AB, Asa SL (2021) The Pangenomic Classification of Pituitary Neuroendocrine Tumors: Quality Histopathology is Required for Accurate Translational Research. Endocr Pathol https://doi.org/10.1007/s12022-021-09671-4
48. Asa SL, Ezzat S (2016) Aggressive Pituitary Tumors or Localized Pituitary Carcinomas: Defining Pituitary Tumors. Expert Reviews Endocrinology and Metabolism 11: 149-162.
49. Mete O, Asa SL (2011) Pathological definition and clinical significance of vascular invasion in thyroid carcinomas of follicular epithelial derivation. Mod Pathol 24: 1545-1552.
50. Asa SL, Kovacs K, Laszlo FA, Domokos I, Ezrin C (1986) Human fetal adenohypophysis. Histologic and immunocytochemical analysis. Neuroendocrinology 43: 308-316.
51. Asa SL, Kovacs K, Horvath E, Losinski NE, Laszlo FA, Domokos I, Halliday WC (1988) Human fetal adenohypophysis. Electron microscopic and ultrastructural immunocytochemical analysis. Neuroendocrinology 48: 423-431.
52. Scheithauer BW, Horvath E, Abel TW, Robital Y, Park SH, Osamura RY, Deal C, Lloyd RV, Kovacs K (2012) Pituitary blastoma: a unique embryonal tumor. Pituitary 15: 365-373.
53. de Kock L, Sabbaghian N, Plourde F, Srivastava A, Weber E, Bouron-Dal Soglio D, Hamel N, Choi JH, Park SH, Deal CL, Kelsey MM, Dishop MK, Esbenshade A, Kuttesch JF, Jacques TS, Perry A, Leichter H, Maeder P, Brundler MA, Warner J, Neal J, Zacharin M, Korbonits M, Cole T, Traunecker H, McLean TW, Rotondo F, Lepage P, Albrecht S, Horvath E, Kovacs K, Priest JR, Foulkes WD (2014) Pituitary blastoma: a pathognomonic feature of germ-line DICER1 mutations. Acta Neuropathol 128: 111-122.
54. Liu APY, Kelsey MM, Sabbaghian N, Park SH, Deal CL, Esbenshade AJ, Ploner O, Peet A, Traunecker H, Ahmed YHE, Zacharin M, Tiulpakov A, Lapshina AM, Walter AW, Dutta P, Rai A, Korbonits M, de KL, Nichols KE, Foulkes WD, Priest JR (2021) Clinical Outcomes and Complications of Pituitary Blastoma. J Clin Endocrinol Metab 106: 351–363. 6000434 https://doi.org/10.1210/clinem/dgaa857
55. Mete O, Lopes MB, Asa SL (2013) Spindle cell oncocytomas and granular cell tumors of the pituitary are variants of pituicytoma. Am J Surg Pathol 37: 1694-1699.
56. Schmid S, Solomon DA, Perez E, Thieme A, Kleinschmidt-DeMasters BK, Giannini C, Reinhardt A, Asa SL, Mete O, Stichel D, Siewert C, Dittmayer C, Hasselblatt M, Paulus W, Nagel C, Harter PN, Schittenhelm J, Honegger J, Rushing E, Coras R, Pfister SM, Buslei R, Koch A, Perry A, Jones DTW, von DA, Capper D, Lopes MB (2021) Genetic and epigenetic characterization of posterior pituitary tumors. Acta Neuropathol 142: 1025-1043. https://doi.org/10.1007/s00401-021-02377-1
57. Cossu G, Daniel RT, Messerer M (2016) Gangliocytomas of the sellar region: A challenging diagnosis. Clin Neurol Neurosurg 149: 122–135. S0303–8467(16)30286–4. https://doi.org/10.1016/j.clineuro.2016.08.002

58. Puchner MJA, Lüdecke DK, Saeger W, Riedel M, Asa SL (1995) Gangliocytomas of the sellar region - a review. Exper Clin Endocrinol 103: 129-149.
59. Asa SL, Mete O (2019) Hypothalamic Endocrine Tumors: An Update. J Clin Med 8. https://doi.org/10.3390/jcm8101741
60. Asa SL, Ezzat S, Kelly DF, Cohan P, Takasumi Y, Barkhoudarian G, Heaney AP, Ridout R, Chik CL, Thompson LDR, Gentili F, Mete O (2018) Hypothalamic Vasopressin-producing Tumors: Often Inappropriate Diuresis But Occasionally Cushing Disease. Am J Surg Pathol 42: 251-260. https://doi.org/10.1097/PAS.0000000000001185
61. Denes J, Kasuki L, Trivellin G, Colli LM, Takiya CM, Stiles CE, Barry S, de CM, Gadelha MR, Korbonits M (2015) Regulation of aryl hydrocarbon receptor interacting protein (AIP) protein expression by MiR-34a in sporadic somatotropinomas. PLoS ONE 10: e0117107. https://doi.org/10.1371/journal.pone.0117107
62. Fukuhara N, Iwata T, Inoshita N, Yoshimoto K, Kitagawa M, Fukuhara H, Tatsushima K, Yamaguchi-Okada M, Takeshita A, Ito J, Takeuchi Y, Yamada S, Nishioka H (2020) Immunohistochemistry or Molecular Analysis: Which Method Is Better for Subtyping Craniopharyngioma? Endocr Pathol. https://doi.org/10.1007/s12022-020-09644-z
63. Brastianos PK, Shankar GM, Gill CM, Taylor-Weiner A, Nayyar N, Panka DJ, Sullivan RJ, Frederick DT, Abedalthagafi M, Jones PS, Dunn IF, Nahed BV, Romero JM, Louis DN, Getz G, Cahill DP, Santagata S, Curry WT, Jr., Barker FG (2016) Dramatic Response of BRAF V600E Mutant Papillary Craniopharyngioma to Targeted Therapy. J Natl Cancer Inst 108. https://doi.org/10.1093/jnci/djv310
64. Nose V, Ezzat S, Horvath E, Kovacs K, Laws ER, Lloyd R, Lopes MB, Asa SL (2011) Protocol for the examination of specimens from patients with primary pituitary tumors. Arch Pathol Lab Med 135: 640-646.
65. Villa C, Vasiljevic A, Jaffrain-Rea ML, Ansorge O, Asioli S, Barresi V, Chinezu L, Gardiman MP, Lania A, Lapshina AM, Poliani L, Reiniger L, Righi A, Saeger W, Soukup J, Theodoropoulou M, Uccella S, Trouillas J, Roncaroli F (2019) A standardised diagnostic approach to pituitary neuroendocrine tumours (PitNETs): a European Pituitary Pathology Group (EPPG) proposal. Virchows Arch . https://doi.org/10.1007/s00428-019-02655-0