Sellar Tumors

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KEYWORDS

• Sella • Pituitary • Adenoma • Hypophysitis • Craniopharyngioma • IgG4 • Pituicytoma • Neurohypophysis

Key points

- Complex sellar anatomy results in a wide spectrum of neoplastic and non-neoplastic entities, including autoimmune processes and secondary involvement by various systemic diseases.
- Magnetic resonance imaging remains a key diagnostic tool.
- Pituitary adenomas are classified according to their developmental lineage (PIT, T-PIT, or SF expression).
- The two histologic variants of craniopharyngioma demonstrate mutually exclusive genetic signatures: *CTNNB1* mutations in adamantinomatous type, and *BRAF V600E mutation* in papillary type.
- Tumors of the posterior pituitary are derived from a common lineage, as all express TTF-1, which can be used as a diagnostic marker.

ABSTRACT

Sellar region lesions include a broad range of benign and malignant neoplastic as well as non-neoplastic entities, many of which are newly described or have recently revised nomenclature. In contrast to other intracranial sites, imaging features are relatively less specific, and the need for histopathological diagnosis is of paramount importance. This review will describe pituitary adenomas, inflammatory lesions, and tumors unique to the region (craniopharyngioma) as well as tumors which may occur in but are not exclusively localized to the sellar location (schwannoma, metastasis, etc.).

PITUITARY ADENOMA

INTRODUCTORY PARAGRAPH

Pituitary adenomas predominantly affect adult men and women in the third to sixth decades, although they occasionally arise in children[1]; rates are higher among Black than White individuals and also higher among Hispanics than non-Hispanics.[2,3] Symptoms reflect local mass effect, including headache, visual deficits, and compression of cavernous sinus structures (notably, cranial nerves III, IV, and VI) as well as hormonal hypersecretion. Hormonal hypersecretion depends on the specific subtype. Elevated prolactin (PRL) levels occur due to "stalk effect," when the mass of a tumor blocks infundibular dopamine release; dopamine inhibits the basally high-secretory tone of lactotrophs, so loss of secretory inhibition results in hyperprolactinemia. Clinical symptoms include amenorrhea and galactorrhea in women and subtle sexual dysfunction and infertility in men. Other hypersecreted hormones result in clinically identifiable phenotypes. A growth hormone (GH)-producing tumor, somatotroph adenoma, yields gigantism before closure of epiphyseal bony plates, acromegaly, soft tissue swelling, hypertension, hyperglycemia, and sleep apnea. An adrenocorticotropic hormone (ACTH)-producing tumor, corticotroph adenoma, causes Cushing disease,

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with elevated cortisol levels leading to central obesity, skin striae, hyperglycemia, osteoporosis, and hirsutism. Tumors secreting follicle stimulating hormone (FSH) and/or luteinizing hormone (LH), gonadotroph adenomas, are usually clinically silent due to the low serum levels of hormone. Thyroid-stimulating hormone (TSH)-producing tumors, thyrotroph adenomas, may cause hyperthyroidism or may arise in the setting of hypothyroidism. Overall, metastasis is rare. When present, either in cerebrospinal or systemic locations, the tumor is designated as pituitary carcinoma. No single set of histologic features is known to accurately predict the metastatic potential of a pituitary adenoma. There is no World Health Organization (WHO) grade assigned to pituitary adenomas in the current system (WHO 2017[4]); the prior version (WHO 2004[5]) suggested the designation of "atypical" based on p53 overexpression and Ki-67 indices, but this is no longer recommended. Instead, pituitary adenomas should be assessed for proliferation (mitotic count and Ki-67 index), tumor invasion, and functional status, features associated with aggressive clinical behavior.[6–9]

The 2017 revision of the WHO classification system of pituitary adenomas also introduced the concept of lineage-specific categorization, as opposed to categorization by the standalone expression of hormones. Three main transcription factors define the categories: PIT-1 (pituitary-specific POU-class homeodomain transcription factor, for differentiation of somatotrophs, lactotrophs, and thyrotrophs); SF-1 (steroidogenic factor 1, regulating gonadotroph cell differentiation), and T-PIT (T-box family member TBX19 transcription factor, for differentiation of corticotrophs).[4]

There is a spectrum of clinically silent to "functional" (hypersecretory) tumors among pituitary adenomas. Serum levels of hormone may not parallel the physical size of the tumor and also, immunohistochemical reactivity does not always reflect the functional status of the tumor.

GROSS FEATURES

MRI is the preferred modality to identify lesions within the pituitary gland and surrounding parasellar region and provides high accuracy.[10] The normal anterior pituitary gland is isointense to gray matter on noncontrast T1- and T2-weighted sequences. The posterior pituitary has intrinsic high T1 signal but is hypointense on T2. The infundibulum and gland progressively enhance with contrast, whereas contrast uptake by pituitary adenomas is slower. Although most of them are solid and enhancing (**Fig. 1**A), they can be sometimes be cystic.

There are two main clinico-radiological grading systems to describe invasion of pituitary adenomas. The Hardy system (1976[11]) grades adenomas by imaging features. Grade I includes microadenomas, intrapituitary lesions less than 1 cm in diameter; grade II describes macroadenomas at least 1 cm in diameter; grade III tumors are locally invasive, causing bony erosion of sella turcica; and grade IV macroadenomas invade extrasellar structures such as bone, hypothalamus, and cavernous sinus. The term "giant pituitary adenoma" is generally reserved for lesions greater than 4 cm in size. The Knosp system (1993[12]) is based on involvement of spaces defined by a medial tangent, the intercarotid line, and a lateral tangent on the intra- and supracavernous internal carotid arteries. Grade 0 represents the normal condition, and grade 4 corresponds to the total encasement of the intracavernous carotid artery. In the original study, most grade 2 and all grades 3 and 4 lesions showed intraoperative evidence of invasion of the cavernous sinus.

Cavernous sinus invasion (CSI) is the most common and significant risk factor for incomplete surgical resection,[13–16] with Knosp grades 3 or 4 all showing CSI.[17] However, because of the imprecision of neuroimaging, intraoperative, and histopathologic evaluation, invasion is not currently part of the formal grading scheme in the most recent WHO classification system.[4]

Grossly, adenomas are soft lesions with a tan-brown discoloration. Microadenomas may be difficult for both surgeon and pathologist to identify grossly.

MICROSCOPIC FEATURES

In contrast to polymorphous cell population of adenohypophyseal tissue arranged in acinar architecture (**Fig. 1**B, C), adenoma is monomorphic with loss of normal acinar architecture (**Fig. 1**D, E). As other neuroendocrine tumors, pituitary adenomas show a multitude of architectural arrangements: diffuse sheets of relatively monomorphic cells, as well as papillary and trabecular patterns. Small mucin-filled cysts found frequently in gonadotroph adenomas as well as other cytologic variants may occasionally pose a diagnostic challenge, especially in small biopsies. Cytologically, tumor cells may be acidophilic, basophilic, or chromophobic. In most cases, the histomorphologic appearance as a standalone is insufficient to subtype the adenoma (see "Diagnosis").

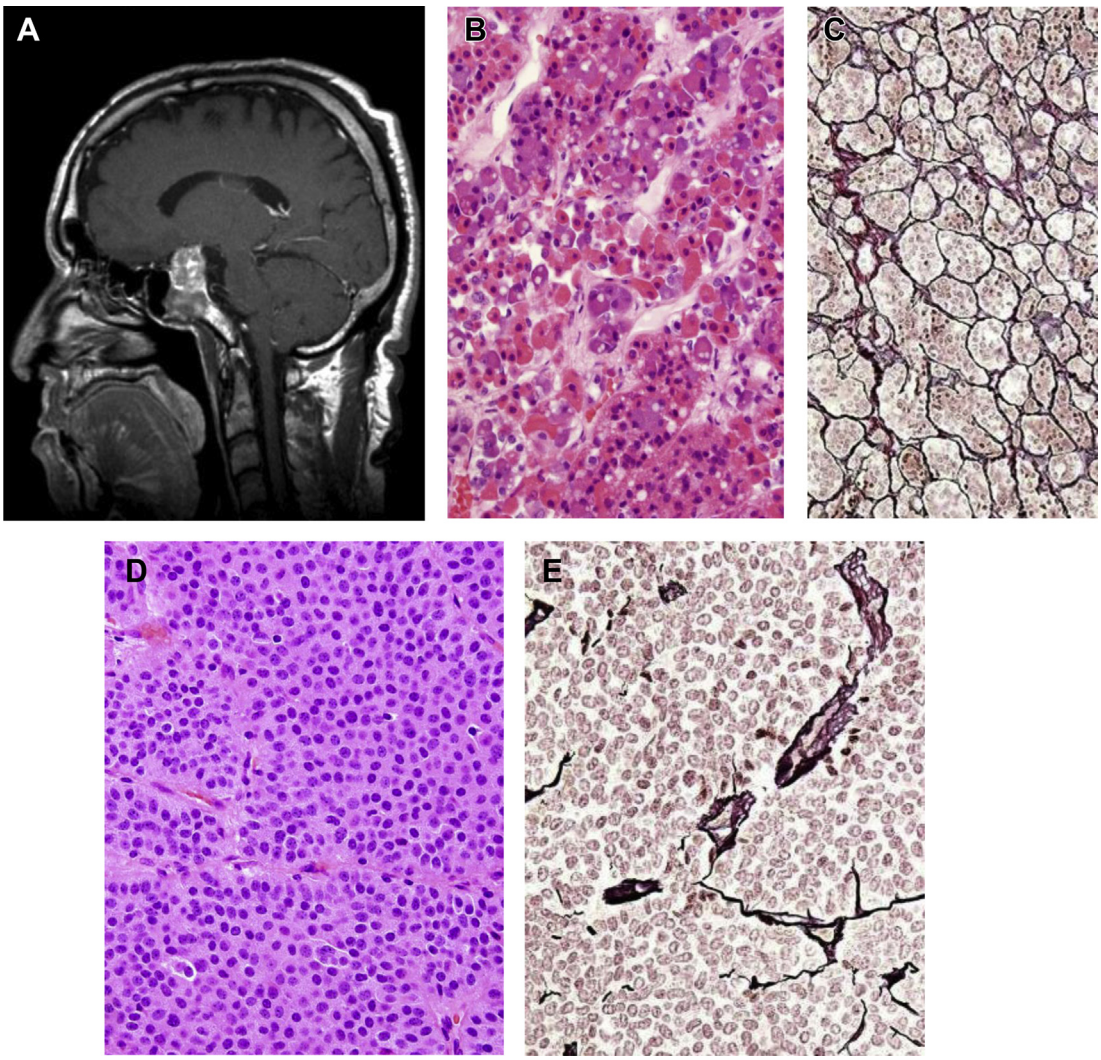

Fig. 1. Contrast-enhancing sellar mass in an adult (*A*). Polymorphous cell population arranged in acinar architecture in adenohypophyseal gland (*B*). Reticulin further accentuates the normal acinar arrangement of normal cells (*C*). The neoplastic cells in adenoma are uniform and monomorphous (*D*) and demonstrate loss of normal acinar architecture as highlighted by a reticulin stain (*E*).

DIFFERENTIAL DIAGNOSIS

Pituitary adenomas may exhibit challenging morphologic features, including clear cell change similar to oligodendroglioma, perivascular pseudorosette architecture similar to ependymoma, pseudopapillary pattern, or nuclear enlargement and hyperchromasia. Fibrosis and small cell–like morphology in some tumors, often following dopamine agonist treatment, can pose diagnostic dilemmas.

DIAGNOSIS

Gonadotroph Adenoma

Gonadotroph adenomas are usually clinically nonfunctioning, indolent tumors found in older adults. Histologically, most are cytologically bland and are arranged in a perivascular or patternless architecture (**Fig. 2**A). Small cysts can sometimes be interspersed.

Positive SF1 immunostaining is sufficient to diagnose gonadotroph adenoma.[18] FSH and LH show patchy or focal reactivity (**Fig. 2**B, C, respectively). Keratin expression may be focal or diffuse.

Hormone-Negative Adenoma (Formerly Null Cell Adenoma)

These tumors are likewise SF1 immunopositive and are histologically similar to gonadotroph adenomas, without FSH or LH reactivity.

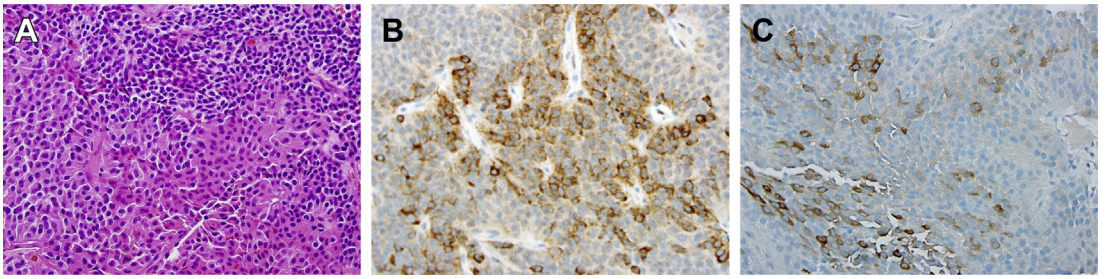

Fig. 2. Gonadotroph adenoma with a biphasic population of tumor cells constituted by a subset of cells with moderate amounts of eosinophilic cytoplasm to the others with scant vacuolated to negligible cytoplasm (*A*). Follicle stimulating hormone (*B*) and luteinizing hormone (*C*) are focally expressed within the tumor cells.

Null Cell Adenoma

A true null cell adenoma, as defined by the 2017 WHO classification[19] is immunonegative for all specific pituitary hormones and all transcription factors.

Growth Hormone Adenoma

The PIT1-driven GH-producing adenomas typically present with clinical symptoms. Two subtypes are based on the electron microscopic features: densely granulated and sparsely granulated.

The densely granulated variant shows a diffuse growth pattern, monotonous cytologic features, and eosinophilic cytoplasm. Immunoreactivity for GH is detectable. Low-molecular-weight keratins fill the cytoplasm. The proliferative index is low, and they are typically macroadenomas.

An "intermediate/mixed/transitional" subtype of GH adenoma has been described, as determined by perinuclear CAM5.2 immunostaining that fills the cytoplasm and contains a smaller number of admixed cells with fibrous bodies or intermediate forms of keratin accumulation.[20] Clinically, these forms respond similarly to somatostatin analogues as the densely granulated variant.

Sparsely granulated GH tumors show a diffuse growth pattern, significant cellular pleomorphism, eccentrically placed nuclei, and paranuclear clearing. The characteristic "fibrous bodies" may be detected on routine stains as pale eosinophilic paranuclear structures (**Fig. 3**A) but are highlighted best by Cam 5.2 immunostaining (**Fig. 3**B). Immunostaining for GH is weak (**Fig. 3**C) or negative. Although the proliferative index may be low, it is a more clinically aggressive subtype as compared with the densely granulated variant.[21]

Mixed Growth Hormone/Prolactin-Secreting Adenoma

These PIT-1-driven, GH-secreting tumors can be subdivided into 3 morphologic types: the mixed GH cell/prolactin (PRL) cell adenoma, the mammosomatotroph cell adenoma, and the acidophilic stem cell adenoma; these mixed tumors behave more aggressively than any pure GH-secreting adenomas, with a lower surgical cure rate.[22] Mixed GH/PRL adenomas are composed of 2 distinct cell types, each of which expresses a unique hormone, as compared with the monocellular mammosomatotroph cell adenomas in which cells coexpress GH and PRL. The distinction is predominantly considered to be clinically unimportant.

Acidophilic Stem Cell Adenoma

This subtype of mixed adenoma is very rare and represents only the minority of GH/PRL-producing tumors.[22,23] Most patients present with symptoms of hyperprolactinemia, and most tumors are rapidly growing macroadenomas with invasive features. Histologically, acidophilic stem cell adenomas show large cytoplasmic vacuoles in an otherwise monomorphous, chromophobic to slightly acidophilic cytoplasm. Oncocytic change with the presence of giant mitochondria is characteristic. Immunoreactivity for PRL and, to a lesser extent, GH is present in the cytoplasm of the same tumor cells. Electron microscopy shows a single, immature population with features of sparsely granulated GH adenoma subtype but contains fewer fibrous bodies. Low serum levels of PRL correspond to their poor response to standard therapies.

Prolactin-Secreting Adenoma

Another, typically clinically functional, PIT1-driven tumor is the prolactinoma (lactotroph adenoma). Most are sparsely granulated, with only rare examples being densely granulated. Prolactinoma in men is associated with aggressive clinical behavior. These tumors usually demonstrate sheeted or interrupted trabecular growth patterns, and more prominent nucleoli, and

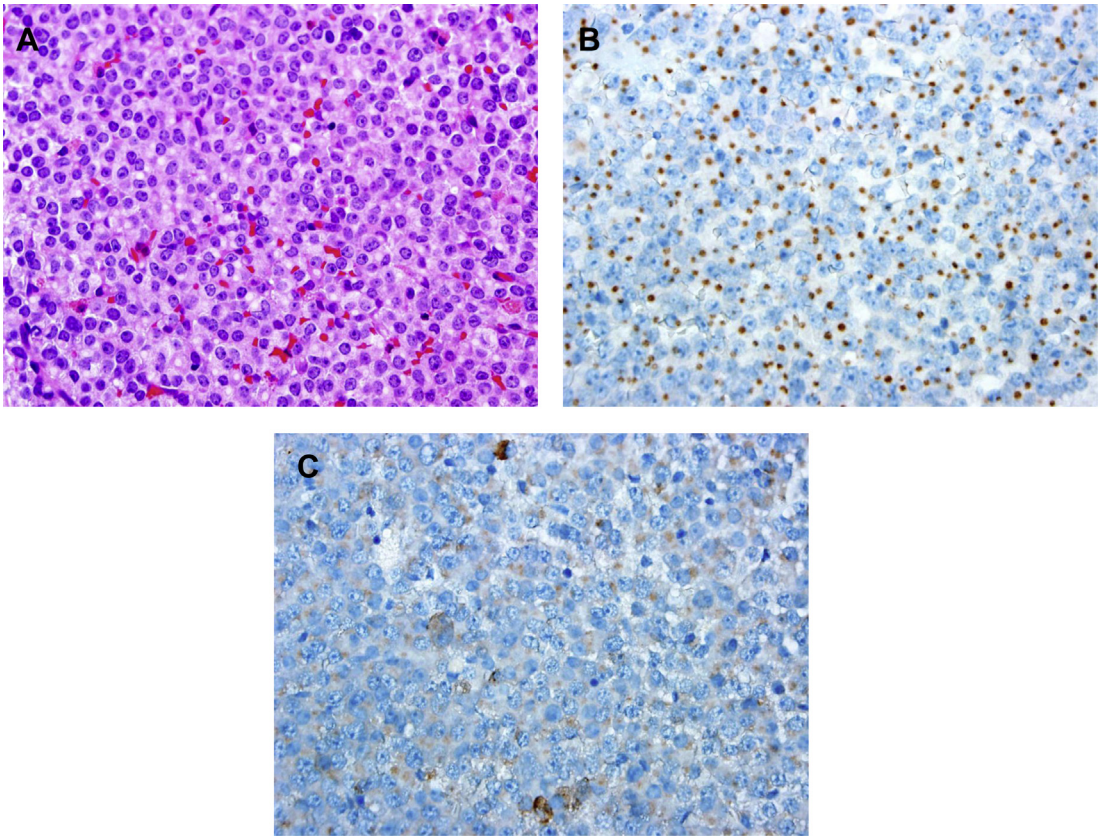

Fig. 3. Sparsely granulated somatotroph adenoma characterized by pale intracytoplasmic "fibrous bodies" (*A*) that are strongly immunoreactive with CAM 5.2 (*B*) and show overall weak expression of growth hormone (*C*).

amphophilic cytoplasm as compared with many other subtypes (**Fig. 4**A). **Fig. 4**B shows an example of PRL immunoreactivity in a diffuse pattern. Depending on the time course of treatment, dopamine agonists may cause dense fibrosis and a "small blue cell" appearance due to apoptosis[24,25] (**Fig. 5**).

Corticotroph Adenoma

TPIT-driven corticotroph adenomas also are subtyped into densely and sparsely granulated. The typical "microadenoma" is a densely granulated ACTH adenoma composed of sheets of monotonous round cells, with abundant basophilic, PAS-positive cytoplasm and strong diffuse immunoreactivity for ACTH (**Fig. 6**). Sparsely granulated ACTH adenomas are more chromophobic, weakly PAS-positive, with less cytoplasmic volume, with more focal ACTH immunoreactivity. The sparsely granulated ACTH adenoma more often is a clinically silent, large, invasive tumor. Slightly confusing is the categorization of 2 silent variants: basophilic, densely granulated (silent type 1) and chromophobic, sparsely granulated (silent type 2).

Crooke cell adenoma is an uncommon variant of ACTH-immunoreactive adenoma in which tumor cells show ringlike, cytokeratin-positive accumulations, to be distinguished from the more common Crooke cell change in adjacent nonadenomatous anterior pituitary gland; Crooke cell change indicates the clinical condition of functional hypercortisolemia. Keratin stain highlights these features.

Corticotroph hyperplasia rarely causes Cushing syndrome and should be carefully evaluated by reticulin stain. A true microadenoma will demonstrate complete loss of acinar architecture. ACTH immunohistochemistry is also necessary.

Thyroid-Stimulating Hormone–Producing Adenoma

Very rarely (~2% of all pituitary adenomas[26]), these PIT1-driven invasive macroadenomas grow in a diffuse pattern with frequent perivascular pseudorosettes. Nuclear pleomorphism and spindled morphology are more common. Extensive fibrosis may be seen. TSH and α-SU are variably immunoreactive.[26,27]

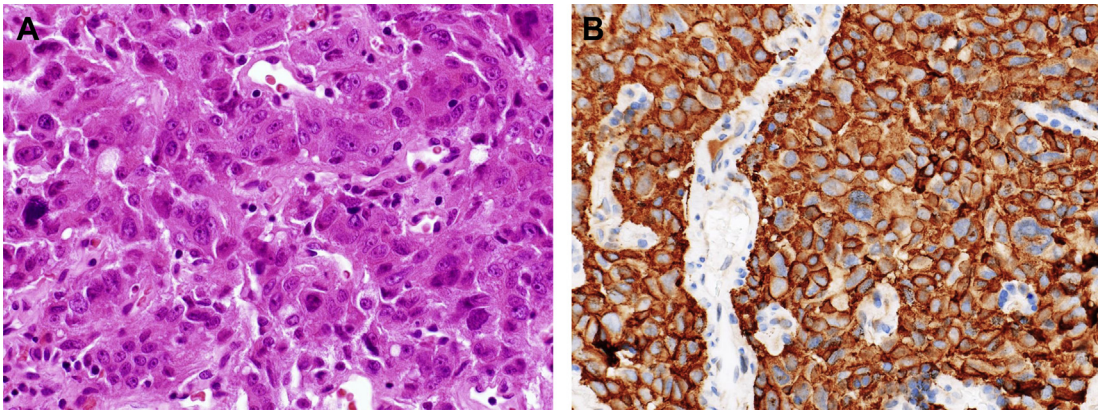

Fig. 4. Prolactinoma. Note the prominent nucleoli, which is a frequent finding in this subtype (*A*). Diffuse and strong reactivity for prolactin in a densely granulated example (*B*).

Plurihormonal PIT1-Positive Adenoma

Previously designated as "silent adenoma subtype 3," the plurihormonal PIT1-positive adenomas are rare tumors, which clinically present with mass effect or signs of hyperthyroidism, acromegaly or galactorrhea, and amenorrhea and are important to recognize given their aggressive clinical behavior.[28] Histologically, they are composed of elongate cells with nuclear spheridia on electron microscopy and show reactivity to GH, PRL, TSH, and α-SU.[26]

Pituitary Apoplexy

Apoplexy describes the clinical situation when hemorrhagic infarction occurs in the sellar region, typically in the setting of pituitary macroadenoma, and sometimes in the post-partum period as a result of physiologic hyperplasia. Sudden-onset symptoms include headache, cranial nerve palsy, or visual disturbances. Histologically, hemorrhagic infarction characterized by ghost outlines of necrotic cells is readily seen (**Fig. 7**A). Reticulin highlights the loss of normal acinar architecture in adenoma (**Fig. 7**B) and its preservation in normal adenohypophyses, and depending on the age of the infarction, tumor cells may retain antigenicity and show reactivity with neuroendocrine markers, ie, synaptophysin and chromogranin (**Fig. 7**C), and keratins, and pituitary hormones.

Mixed Pituitary Adenoma-Gangliocytoma

This tumor, generally considered to represent neuronal metaplasia of adenoma cells, shows a variety of histologic patterns, although the clinical, neuroimaging, and intraoperative presentation is that of a pituitary adenoma without any prognostic connotation. Notably, it harbors large dysmorphic ganglionic cells (**Fig. 8**) that are frequently reactive with neuronal markers and negative with glial markers. The two components may be sharply demarcated or variably admixed with predominance of adenoma. Transitional tumor cells or mature ganglion cells may be immunoreactive for pituitary hormones or transcription factors, consistent with a metaplastic process rather than a "collision tumor."[29]

PROGNOSIS

Both medical and surgical approaches are used for the management of pituitary adenoma,

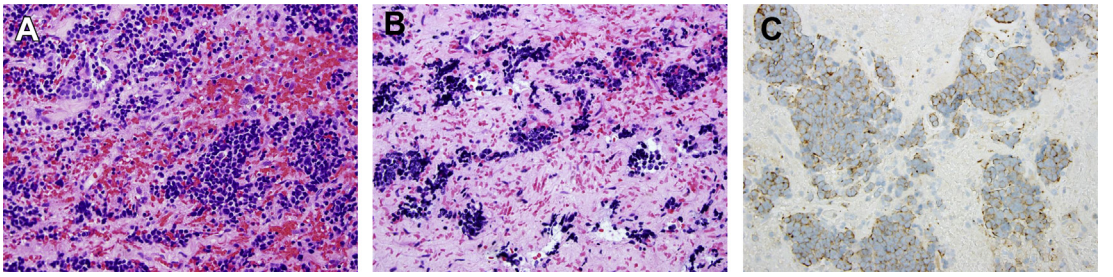

Fig. 5. Prolactinoma from a patient who was medically treated with carbegoline demonstrating "small cells" with minimal cytoplasm, high nuclear-cytoplasmic ratio, and hyperchromatic nuclei (*A*) as well as stromal fibrosis (*B*). Punctate staining pattern seen with prolactin (*C*).

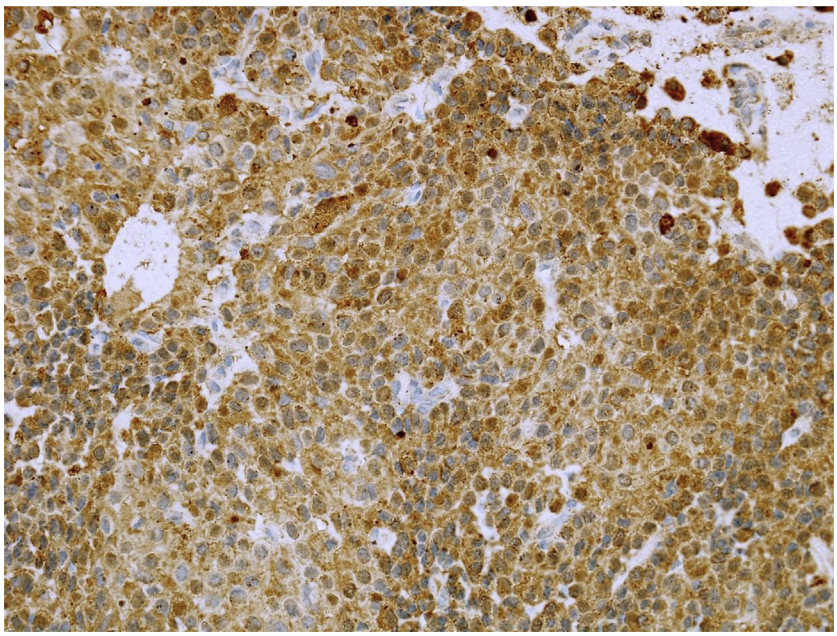

Fig. 6. Densely granulated ACTH-secreting adenoma that is strongly immunoreactive with ACTH.

depending on the subtype. Most prolactinomas respond to dopamine receptor agonists, particularly those with hypersecretion of prolactin. Somatotroph adenomas are treated with somatostatin analogues (octreotide), and in the case of sparsely granulated subtypes, GH receptor antagonist (GHRH) antagonists are an adjuvant therapy.

Surgical management, including transsphenoidal/translabial and endoscopic transnasal approaches, aims to resect as much tumor as possible. For intrasellar tumors, the transsphenoidal or endonasal endoscopic techniques show similar results but for larger extrasellar tumors the endonasal approach may be preferred. A transfrontal approach may be required to decompress the visual pathways for larger tumors.

Complications of surgery include cerebrospinal fluid (CSF) leak, residual tumor, postoperative diabetes insipidus, and apoplexy in residual adenoma.

If a resection is subtotal, outcome is also related to any residual hypersecretory endocrinopathy.

Determination of subtype helps both prognosticate and predict response to therapy. Well-differentiated adenomas respond better, such as prolactinomas with dopamine agonists and densely granulated GH adenomas with somatostatin analogues. In the case of the sparsely granulated GH adenomas, a switch from somatostatin analogue to GHRH, or addition of GHRH, may show improved response.

Conventional radiation or radiosurgery is considered for recurrent and/or invasive, aggressive adenomas; subtyping does not necessarily mandate the use of radiation.

OVERVIEW: MOLECULAR PATHOLOGY OF PITUITARY ADENOMAS

Pituitary adenomas are most commonly sporadic, and in most, the primary genetic defect is

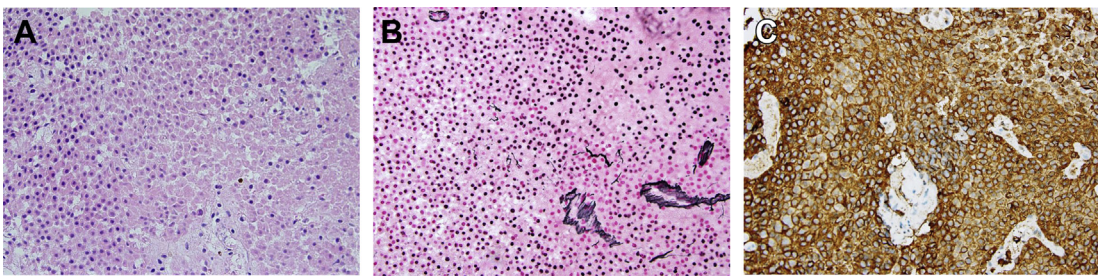

Fig. 7. Large areas of necrosis, characterized by "ghost outlines" of tumor cells, are pathognomic of apoplexy (*A*). Lack of normal acinar architecture is supported by a reticulin stain (*B*). There is strong and diffuse chromogranin immunoreactivity despite extensive necrosis, which suggests preserved antigenicity in a subset of apoplectic cases (*C*).

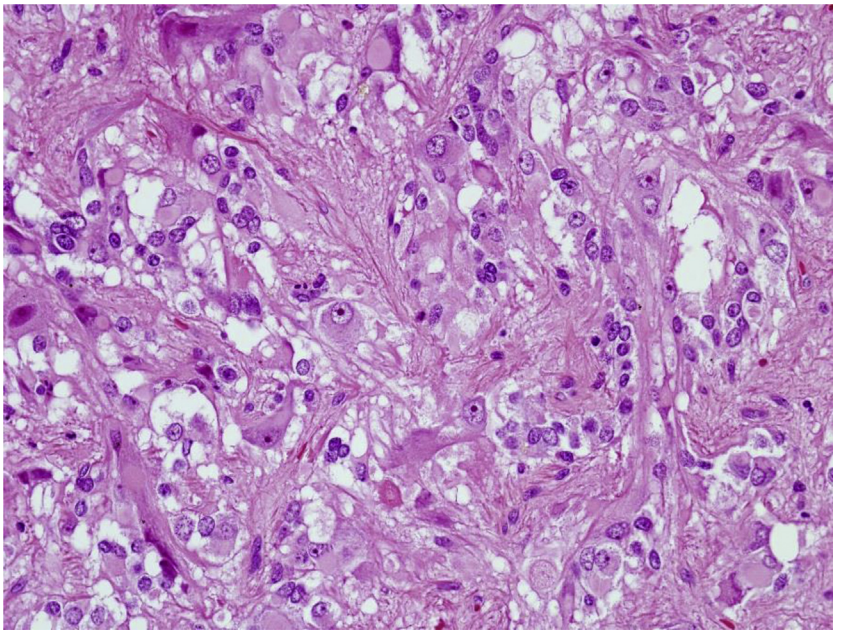

Fig. 8. Neuronal differentiation is an unusual phenomenon in pituitary adenoma. Several dysmorphic neuronal elements, including some large forms akin to ganglion cells, are seen.

unknown. Somatic mutations in the *GNAS* gene are found in 40% of somatotroph adenomas, 10% of clinically nonfunctioning pituitary adenomas, and in 5% of corticotroph adenomas.[30–32] Nonsyndromic gigantism has been related to inactivating germline mutations on the AIP gene and more recently to germline or somatic duplication of the *GPR101* gene.[33–35] Mutations in the *USP8* gene are identified in 36% to 62% of sporadic corticotroph adenomas.[30–32]

Other oncogenes and tumor suppressor genes that have been shown to be linked to pituitary tumorigenesis, progression, and malignant transformation include the oncogene pituitary tumor-transforming gene, the protooncogene *H-ras*, and the tumor suppressor genes *RB* and *TP53*.[30–32]

ASSOCIATED GENETIC CHANGES/ ALTERATIONS

Although most pituitary adenomas are sporadic, some well-known hereditary conditions are associated with pituitary adenomas: multiple endocrine neoplasias 1 and 4 (MEN1 and MEN4); the Carney complex, related to mutations of the tumor suppressor gene *PRKAR1A*; McCune-Albright syndrome, related to activating mutation of the gsp oncogene; SDH-related hereditary pheochromocytoma/paraganglioma syndrome; isolated familial somatotrophinoma (IFS), associated with a loss of heterozygosity at the 11q13 locus but not with the *MEN1* gene; familial isolated pituitary adenoma (FIPA) syndrome; and X-linked acrogigantism (XLAG), associated with GPR101 microduplication. The syndromic tumors tend to be somatotroph or lactotroph adenomas. In addition, the rare embryonal-like pituitary blastoma occurs in the setting of *DICER1* mutation in infants or young children.[36]

Pathologic Key Features—Pituitary Adenomas

Commonly seen in adults, solid and/or cystic enhancing sellar mass, rarely can be parasellar in ectopic tissue; loss of normal acinar architecture, which can be highlighted by reticulin stain; monomorphic cell population; typically low proliferation indices; acute presentation in patients with apoplexy

Infrequent in children and adolescents with predilection for latter

Current classification based on lineage-specific markers: SF (gonadotroph adenomas), PIT (lactotroph, somatotroph, mixed GH/PRL, TSH-producing, and plurihormonal adenomas), and T-PIT (corticotroph adenomas); lack of hormone or transcription factor expression is designated "null cell adenoma"

Hormone-producing tumors produce clinical symptoms (eg, somatotroph, corticotroph, lactotroph adenomas) versus clinically silent tumors; a spectrum exists

Assess mitotic rate, proliferative activity, and invasion; "atypical" designation (WHO 2004) no longer recommended (WHO 2017)

Clinically more aggressive subtypes include sparsely granulated GH tumors, mixed GH/PRL-secreting adenomas, acidophilic stem cell adenoma, and plurihormonal PIT1-positive adenoma (formerly "silent adenoma subtype 3")

A minority of tumors occur in syndromic settings: MEN1, MEN4, Carney complex, McCune-Albright syndrome, SDH-related hereditary pheochromocytoma/paraganglioma syndrome, IFS, familial isolated pituitary adenoma (FIPA) syndrome, and XLAG; syndromic tumors tend to be GH or PRL adenomas

HYPOPHYSITIS

INTRODUCTION

Hypophysitis, or inflammation of the pituitary gland, describes a spectrum of underlying causes and can generally be classified as primary or secondary; latter can be seen in association with sarcoidosis, Sjogren syndrome, granulomatosis with polyangiitis (GPA; Wegener disease), Langerhans cell histiocytosis (LCH), and Erdheim-Chester disease.

Primary hypophysitis occurs in approximately equal proportions of men and women and is commonly associated with other autoimmune disorders, particularly thyroid disorders (Hashimoto thyroiditis and Grave disease). The most common infiltrate is lymphocytic, and less commonly granulomatous and xanthomatous inflammation may be seen. Secondary causes of granulomatous hypophysitis include tuberculosis, sarcoidosis, syphilis, LCH, GPA, and Rathke Cleft Cyst (RC) rupture.

In the new era of checkpoint inhibitor and other immune therapies, there is an emerging class of immunotherapy-associated hypophysitis, which often presents with headache and anterior hypopituitarism.[37] The degree of pituitary enlargement is typically mild, and compression of the optic apparatus is very rare. Unlike other forms of hypophysitis, diabetes insipidus is unusual in patients with immunotherapy-associated hypophysitis. Of note, no case of immunotherapy-associated hypophysitis has been confirmed by pituitary gland biopsy.[37]

Reversible or irreversible hypopituitarism may be a rare side effect following treatment with interferon-α, and interferon-α/ribavirin combination therapy has been associated with cases of granulomatous hypophysitis with anterior pituitary dysfunction.[38] Very recently, the antiinterleukin-12, and -23 monoclonal antibody ustekinumab (in treatment of psoriasis) has been associated with a case of hypophysitis with panhypopituitarism.[39]

GROSS FEATURES

Because the inflammatory infiltrate typically presents as a mass lesion, imaging studies may suggest pituitary adenoma due to homogeneous contrast-enhancement (**Fig. 9**A), and the patient is referred for surgery. Intraoperative diagnosis by touch or smear preparations and frozen section dictates the extent of resection, which would be undertaken for decompressive measures.

MICROSCOPIC FEATURES

Lymphocytic hypophysitis is an infiltration of the anterior pituitary by lymphocytes, including reactive follicles, plasma cells, and variable amounts of fibrosis. Necrosis can be either nonspecific or specific for certain cell types. Granulomatous hypophysitis is composed of histiocytes, multinucleated giant cells, and lymphoplasmacytic inflammation (see **Fig. 9**B). Immunostains for neuroendocrine markers, ie, synaptophysin and chromogranin (see **Fig. 9**C), as well as lymphocyte markers (pan-lymphocyte: CD45 {see **Fig. 9**D}; T-cell: CD3; B-cell: CD20), and histiocytic markers aid in characterizing this process further. Xanthomatous inflammation also contains S100- and CD1a-negative histiocytes (predominant), lymphocytes, variable granuloma formation, and acellular eosinophilic debris.

DIFFERENTIAL DIAGNOSIS

The histologic differential diagnosis includes lymphoma, immunoglobulin G4 (IgG4)-related disease (discussed later in this article), infectious process, secondary changes related to a ruptured Rathke cleft cyst, and organization associated with pituitary apoplexy.

DIAGNOSIS

Diagnosis is based on a combination of clinical, imaging, and histopathologic features.

PROGNOSIS

Primary hypophysitis can be self-limiting, and spontaneous remission may occur, although rigorous studies of the disease are lacking given its rarity. Primary hypophysitis frequently evolves

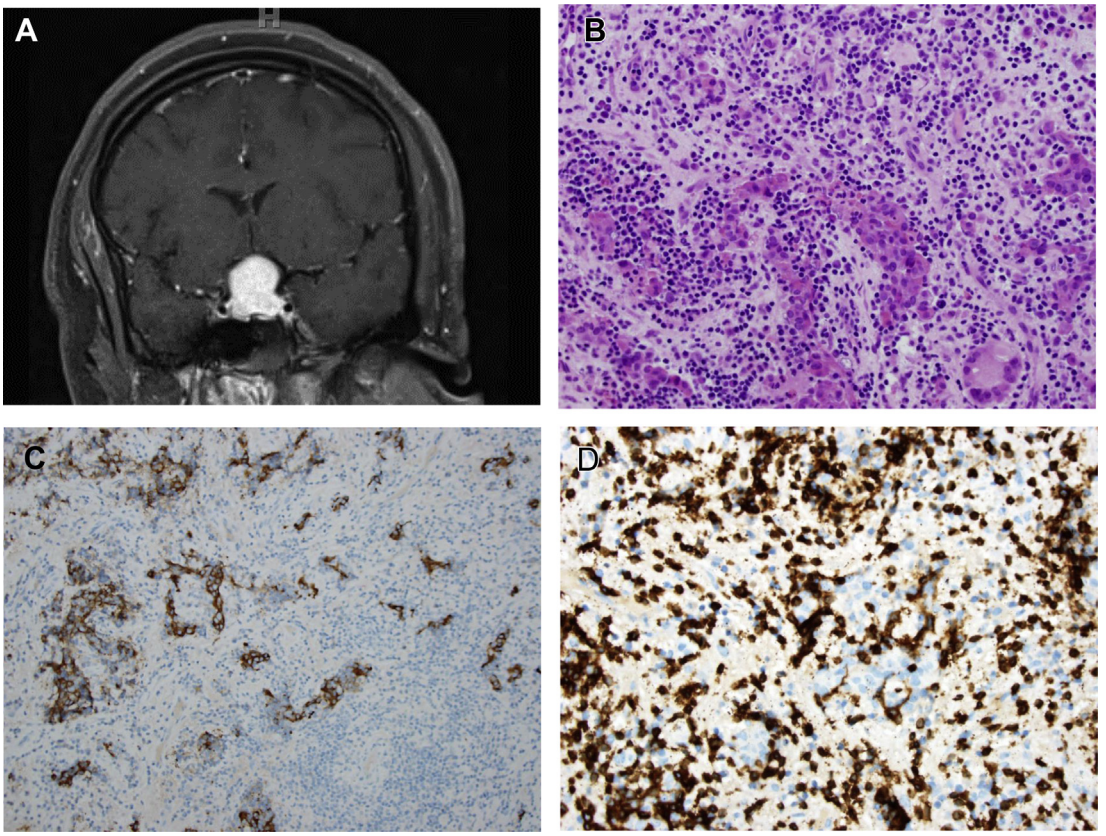

Fig. 9. Granulomatous hypophysitis. Homogeneously solid contrast-enhancing lesion on MRI is usually mistaken for a pituitary adenoma (*A*). Exuberant chronic inflammatory cell infiltrate with invasion of the residual acini along with scattered multinucleate giant cells and fibrosis in the background (*B*). The residual adenohypophyseal tissue can be highlighted by a chromogranin (*C*) or synaptophysin. CD45 stains lymphocytes in the abundant chronic inflammatory cell infiltrate (*D*).

to fibrosis, pituitary atrophy, and may result in "empty sella."[40] Most patients will require long-term hormone replacement. It is unknown whether glucocorticoid treatment is effective. As such, conservative management is recommended for primary hypophysitis unless symptoms are severe and progressive. High-dose glucocorticoids are the first-line treatment to improve the swelling of the pituitary and improve the symptoms related to significant sella compression. The presence of central diabetes insipidus is a poor prognostic factor for response to glucocorticoids. Glucocorticoid therapy is less effective in granulomatous or xanthomatous hypophysitis. In cases of glucocorticoid-resistant hypophysitis, azathioprine, methotrexate, cyclosporine A, and rituximab have been used successfully.[40,41] Surgery is considered only in cases with serious and progressive deficits of the visual field, visual acuity, or nerve paralysis not responsive to medical treatment. Progression/relapse occurs in 11% to 25% of patients at mean 3-year follow-up.[41] Recovery rates of visual deficits related to chiasmal compression are also low. Finally, stereotactic radiotherapy has been effectively used in selected patients who have failed medical treatment or suffer from repeated recurrence of lymphocytic hypophysitis.[42]

Pathologic Key Features—Hypophysitis

Primary versus secondary types

Primary hypophysitis often associated with another autoimmune diseases; lymphocytic > granulomatous > xanthomatous

Rare examples associated with checkpoint inhibitor or other targeted therapies

ΔΔ *Differential Diagnosis—Hypophysitis*

Pituitary apoplexy

Lymphoma

IgG4-related disease

Infection

IMMUNOGLOBULIN G4 DISEASE: DURAL BASED AND/OR INVOLVEMENT OF PITUITARY GLAND

INTRODUCTION

IgG4-related disease (IgG4-RD), a fibroinflammatory disease that preferentially affects pancreas, salivary gland, the orbit, lymph nodes, lung, and kidney, may also involve the sellar region. It may present as a mass or diffusely infiltrative lesion. IgG4-RD hypophysitis shows a female:male ratio of 2.4:1.[43] Intracranial IgG4-RD presents as pachymeningitis or hypophysitis and generally does not affect the brain parenchyma. When the pituitary gland or stalk is affected, signs include hypopituitarism, diabetes insipidus, or local mass effect.

GROSS FEATURES

There is a wide spectrum of imaging and gross features attributable to IgG4-RD, most of which are nonspecific for the entity. MRI is the modality of choice. Typically, imaging shows an enlargement of the pituitary gland or mass lesion of the pituitary, at times causing optic chiasm compression, thickened pituitary stalk, or mass formation in the infundibulum. Disappearance of physiologic posterior pituitary bright spot on T1-weighed image is also common. Cystic formation in the enlarged anterior pituitary or "empty sella" has also been described, and the diagnosis is often omitted in the radiologic differential, particularly when serum levels of IgG4 are normal.[44]

MICROSCOPIC FEATURES

IgG4-RD is manifest histologically by a lymphoplasmacytic infiltrate with an increased number of plasma cells, predominantly of the IgG4 subtype, storiform fibrosis, and obliterative phlebitis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis, on imaging and histopathologic examination, includes mass-forming lesions and some immune-mediated diseases (eg, Churg-Strauss syndrome, multicentric Castleman disease, sarcoidosis, Sjogren syndrome). Histopathologic examination should help to establish the diagnosis. Lymphocytic hypophysitis may closely mimic IgG4-RD; although both entities are characterized by a lymphoplasmacytic infiltrate, the latter shows a predominance of plasma cells, whereas the former shows admixed B and T lymphocytes in greater proportion.

DIAGNOSIS

In conjunction with imaging features, a diagnosis of IgG4-RD may be rendered based on the histopathologic examination as well as high serum IgG4 and IgG4/IgG ratio, although the serum markers are elevated in ~70% of patients. Guidelines for diagnosis of IgG4-related disease in general were proposed in 2011, revised in 2017.[45,46] According to the guidelines, (1) typical organ involvement, (2) serum IgG4 level, and (3) histopathological findings are used for diagnosis, where (1) + (2) + (3) indicates definite, (1) + (2) indicates possible, and (1) + (3) indicates probable. For intracranial cases, Lindstrom and colleagues[47] first proposed application of the consensus criteria (≥10 IgG4-positive cells/HPF as minimum criteria for the diagnosis). Leporati proposed specific criteria for the diagnosis of IgG4-RD hypophysitis.[48]

	Criterion	Diagnosis
1	Mononuclear infiltration of the pituitary gland, rich in lymphocytes and plasma cells, with >10 IgG4-positive cells/high-power field	Criterion 1 Or Criteria 2 + 3 Or Criteria 2 + 4 + 5
2	Sellar mass or thickened pituitary stalk by MRI	
3	Biopsy-proven involvement in other organs	
4	Serum IgG4 level >140 mg/dL (1.4 g/L)	
5	Shrinkage of the pituitary mass and symptom improvement with corticosteroids	

PROGNOSIS

Spontaneous improvement is very rare, and most of the cases show slow and indolent progression. IgG4-RD should be promptly treated with

glucocorticoids, which often cause remission within a few weeks. However, long-term maintenance glucocorticoid therapy, with or without a steroid-sparing agent, may be required. Relapse is possible and multiple courses of high-dose glucocorticoids are often necessary. Rituximab and azathioprine have also been reported to be effective.

Pathologic Key Features—IgG4-Related Disease

An autoimmune disease that may affect other organs, IgG4-related disease is manifest in the sellar region as hypopituitarism, diabetes insipidus, or mass effect

May present as a pachymeningitis or hypophysitis

Diagnosis requires a combination of histopathologic, radiologic, and serologic criteria

Histopathologic features include more than 10 IgG4-positive cells/high-power field within a lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis

RATHKE CLEFT CYST

INTRODUCTION

Rathke Cleft Cysts (RC) are benign, epithelium-lined intrasellar cysts that originate from remnants of the Rathke pouch. They are found in 13% to 33% of the general population and can compress adjacent structures, causing symptoms such as headaches, vision problems, or pituitary hormone deficits.

Most radiologically diagnosed RCs may be managed conservatively, because they are statistically unlikely to increase in size or cause symptoms.

However, among patients who present with sellar and suprasellar lesions in neurosurgical series, RCs account for 6% to 10%.

GROSS FEATURES

RCs commonly have a round, ovoid, or dumbbell shape on imaging studies, given their location between anterior and posterior gland. On computed tomography (CT) scan, they are well-circumscribed, hypoattenuating, cystic sellar masses that may extend into the suprasellar region.[49] Because of the variability of cyst contents, RCs are either isoattenuating or hyperattenuating relative to the brain parenchyma. Typically, there is a thin wall that may enhance. Extravasation of cystic contents may also cause enhancement. Complex cysts may have septations. Large cysts may cause bone remodeling.

MRI appearances of RCs are highly variable but can be roughly categorized into 2 patterns: those with low intensity on T1-weighted and high intensity on T2-weighted images, and those with high intensity on T1-weighted images and variable intensity on T2-weighted images. Most are homogenous, as opposed to other lesions, such as craniopharyngioma, which are more heterogeneous. However, the features on standard sequences of cystic lesions (RC, craniopharyngioma, and hemorrhagic and cystic pituitary adenomas) often overlap. Data suggest that a RC may be differentiated from a craniopharyngioma or a hemorrhagic pituitary adenoma using special diffusion-weighted imaging techniques.[50]

MICROSCOPIC FEATURES

Given their location between anterior and posterior pituitary, the cyst wall may be adjacent to normal components of these structures. The lining ranges from low cuboidal to tall columnar, sometimes with mucinous differentiation (**Fig. 10**), consistently reactive for pan-cytokeratin. Cilia are present on high-power magnification. The lining may also undergo squamous metaplasia. RCs often contain colloid-like, eosinophilic, amorphous mucin.

DIFFERENTIAL DIAGNOSIS

Squamous metaplasia may be confused for papillary craniopharyngioma in a small biopsy; BRAF V600E immunohistochemistry may help to distinguish the two. An epidermoid cyst may be considered, although the presence of a keratohyaline layer and flaky keratin content will distinguish it from RC.

DIAGNOSIS

Neuroimaging studies alone, given the variability in presentation, are often insufficient to make a definitive diagnosis. The neuroimaging differential includes arachnoid cyst, epidermoid cyst, craniopharyngioma, or pituitary adenoma. Tissue diagnosis remains a gold standard.

PROGNOSIS

The outcome of a symptomatic RC is related to anterior pituitary dysfunction, central diabetes insipidus, visual deficits, and other symptoms related to mass effect, and possibly the granulomatous, xanthomatous, and lymphocytic

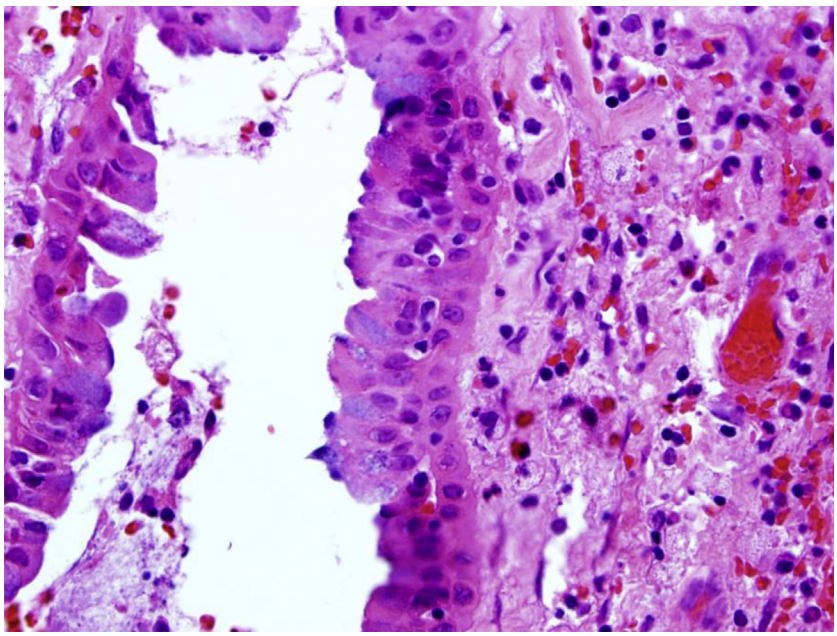

Fig. 10. Presence of a cyst lining with ciliated low cuboidal to columnar epithelium with or without mucinous cells characterizes Rathke Cleft Cyst (RC). This particular example shows scattered intracytoplasmic mucin.

hypophysitis theorized to occur after rupture of RC.[51–53] Symptoms resolve in most of the patients following surgical resection, although diabetes insipidus may persist.[54]

***Pathologic Key Features* – Rathke Cleft Cyst**

Simple or complex cyst arising from the Rathke cleft remnant lined by cuboidal, columnar, or attenuated respiratory epithelium may undergo squamous metaplasia and contains eosinophilic- or colloid-like contents.

CRANIOPHARYNGIOMA

INTRODUCTION

Craniopharyngiomas are WHO grade I, circumscribed epithelial tumors that most commonly arise in the suprasellar region. Craniopharyngioma comprises 5% to 10% of all childhood brain tumors and 1.2% to 4.6% of brain tumors in adults.[3] The peak incidence is in children aged 0 to 19 years. A second peak occurs later in life, between ages 40 and 79 years. There is no sex predilection.

Craniopharyngioma comprises 2 clinically, histologically, and biologically distinct subtypes: adamantinomatous (most common) and papillary. Rare hybrid forms have also been reported, even with the characteristic genetic signatures (see later discussion).[55] Papillary craniopharyngioma occurs almost exclusively in adults, whereas adamantinomatous craniopharyngioma occurs in both adults and children.

The close histopathologic and immunohistochemical resemblance among adamantinomatous craniopharyngioma, adamantinoma of the jaw, and calcifying odontogenic cyst suggests an odontogenic epithelial differentiation for these tumors.[56] Collision lesions of craniopharyngioma with, most commonly, pituitary adenoma, have been described.[57,58]

The current hypothesis is that pituitary adenoma, adamantinomatous craniopharyngioma, and Rathke cyst share a common ancestry from involuted remnants of the Rathke pouch and the craniopharyngeal duct.[59] In elderly persons, squamous metaplasia of adenohypophyseal cells of the pituitary stalk or gland has been postulated as a possible origin for the papillary variant of craniopharyngioma.[60]

Clinical features of craniopharyngiomas may include visual disturbances (from compression of the optic chiasm and adjacent nerves and tracts), endocrine abnormalities, including diabetes insipidus, and signs of increased intracranial pressure. Cognitive and personality changes have also been observed.

GROSS FEATURES

MRI typically shows an adamantinomatous craniopharyngioma as a complex solid/cystic lesion with

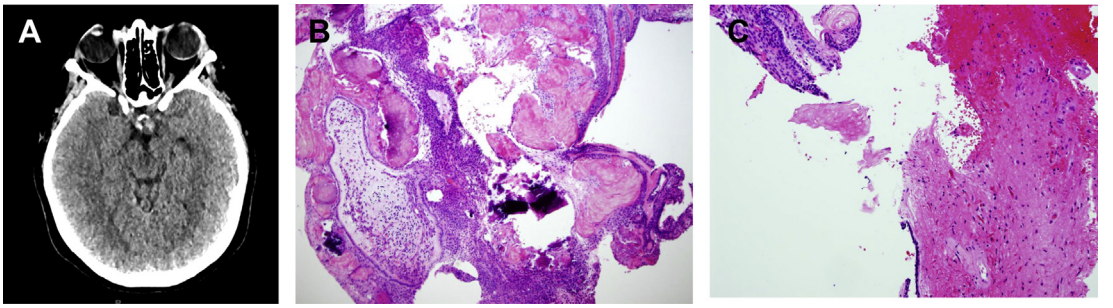

Fig. 11. Peripheral calcifications of adamantinomatous craniopharyngioma are a helpful feature in their diagnosis on CT scan (*A*). Wet keratin, peripheral palisading, stellate reticulum, and dystrophic calcifications are variably present on histologic examination (*B*). Piloid gliosis with numerous Rosenthal material is often seen at the periphery of adamantinomatous craniopharyngioma and can be a diagnostic pitfall during intraoperative consultation (*C*).

heterogeneous signal intensity. The cysts are often filled with fluid of high protein content and are hyperintense on T1-weighted images. Solid areas enhance. Peripheral calcification is often prominent on CT scans (**Fig. 11**A).

Adamantinomatous craniopharyngioma is a partly cystic mass filled with dark greenish-brown fluid that has traditionally been compared in terms of color and consistency with "machinery oil." The characteristic white speckled appearance of "wet" keratin nodules typical of the adamantinomatous variant is frequently seen on gross examination.

MRI of a papillary craniopharyngioma characteristically depicts an enhancing, predominantly solid, circumscribed mass without the calcification or complex cystic architecture of the adamantinomatous variant. The papillary architecture may sometimes be evident.

In contrast to the adamantinomatous variant, which tends to insinuate tongues around nerves and blood vessels, the papillary subtype is comparatively well circumscribed and typically lacks the complex multicystic architecture and fluid-filled spaces.

Although the imaging descriptions of the 2 morphologic variants are typically described as earlier, note that overlap and exceptions occur. In addition, there is overlap between the imaging characteristics of craniopharyngiomas of both subtypes and other sellar/suprasellar mass lesions of this anatomic neighborhood; thus, tissue examination is generally required for definitive diagnosis.

MICROSCOPIC FEATURES

With adamantinomatous craniopharyngiomas, a complex epithelial lesion with cysts and calcified "wet" keratin is seen. The epithelium has central stellate reticulum with prominent peripheral palisading. Rarely, ciliated cells and goblet cells are encountered. Even more rare is enamel formation in an abortive attempt to form "toothlike" structures (**Fig. 11**B). The adjacent neural parenchyma may show granulomatous reaction with cholesterol clefts. In some cases, there is perilesional piloid gliosis with Rosenthal fibers (**Fig. 11**C). A biopsy or frozen section sample from this area can be potentially misleading.

With papillary craniopharyngiomas, an epithelial lesion composed of mature squamous epithelium without surface maturation, a keratohyaline granular layer, or keratin formation is noted (**Fig. 12**A). Focal tissue dehiscence with resultant pseudopapillary architecture is often present, as are small whorls. Although basal peripheral palisading is also seen, this feature is not as prominent as with the adamantinomatous variant. The most characteristic features of the adamantinomatous subtype are absent, including nodules of "wet" keratin, "stellate reticulum," and calcification. Rarely, ciliated epithelium and goblet cells may be encountered. Immunostain for BRAF (V600E) tends to be positive (**Fig. 12**B).

DIFFERENTIAL DIAGNOSIS

The histopathologic differential includes epidermoid cyst, possibly germinoma, Rathke cleft cyst with squamous metaplasia, and pilocytic astrocytoma (in areas of surrounding piloid gliosis) in small biopsy samples.

DIAGNOSIS

Craniopharyngioma tumor cells display immunoreactivity to epithelial membrane antigen (EMA) and cytokeratin. Most adamantinomatous craniopharyngiomas show aberrant nuclear expression of beta-catenin, a feature that is not typically observed in papillary craniopharyngiomas.[61] In contrast, most papillary craniopharyngiomas harbor BRAF V600E mutation, which can be demonstrated immunohistochemically.[62]

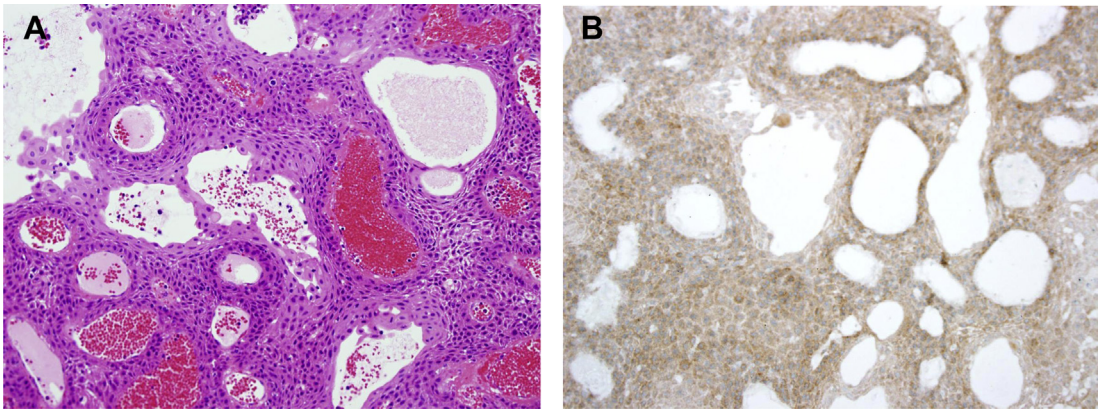

Fig. 12. Papillary craniopharyngioma. Well-differentiated stratified squamous epithelium with pseudopapillary architecture and lacking keratohyaline granules with pseudopapillary architecture (*A*). Reactivity with BRAF (V600E) immunostain is a frequent finding and can help distinguish with its close mimics such as epidermoid cyst (*B*).

PROGNOSIS

Craniopharyngioma is managed by 1 of 2 strategies: (1) attempted gross total resection or (2) a planned subtotal resection followed by radiotherapy or other adjuvant therapy. No established guidelines exist regarding management of craniopharyngioma. Radiation therapy includes external fractionated radiation, stereotactic radiation, or brachytherapy. In addition, bleomycin may be considered for local intracystic chemotherapy, particularly in children.[63]

Neuropsychological deficits represent the major limiting factor for independent social functioning. The degree of psychosocial impairment correlates directly with the degree of hypothalamic injury sustained at the time of surgery. In some patients, deficits are related to radiation injury.

Panhypopituitarism is reported in most of the patients. Most patients require multiple hormonal supplements and adjustments during long-term follow-up. Other prevalent morbidities include neurologic, psychosocial, and cardiovascular abnormalities.

OVERVIEW: MOLECULAR PATHOLOGY OF CRANIOPHARYNGIOMA

Most of the adamantinomatous craniopharyngiomas harbor a mutation of the beta-catenin gene (*CTNNB1*). Almost all mutations involve exon 3, which encodes the degradation targeting box of beta-catenin. This mutation results in nuclear accumulation of beta-catenin protein and dysregulation of the Wnt signaling pathway, with activation of downstream targets such as Axin-2. Papillary craniopharyngiomas and other sellar region lesions do not exhibit this mutation.

BRAF V600E mutations have been demonstrated in up to 95% of papillary craniopharyngioma cases.[32] This is a well-studied activating mutation of a serine-threonine kinase involved in cell division and differentiation via the MAP-kinase/ERK signaling pathway, which has been implicated in a variety of other neoplasms including melanoma, colorectal carcinoma, and papillary thyroid carcinoma.

A study reported 2 cases of adamantinomatous craniopharyngioma exhibiting *BRAF V600E* mutations; however, in both cases a concomitant *CTNNB1* mutation was also present.[55] In most cases, however, BRAF V600E and beta-catenin alterations segregate by subtype.

ASSOCIATED GENETIC CHANGES/ ALTERATIONS

Relatively recent studies have also demonstrated that papillary and adamantinomatous craniopharyngiomas have distinct DNA methylation profiles.[64] Chromosomal imbalances are very rare in both subtypes.[65,66]

Pathologic Key Features—Craniopharyngioma

Two types: adamantinomatous (adults and children, *CTNNB1* mutations), and papillary (adults, *BRAFV600E* mutations)

Adamantinomatous variant: a complex epithelial lesion with cysts and calcified "wet" keratin; central stellate reticulum with prominent peripheral palisading

Papillary variant: epithelial lesion composed of mature squamous epithelium without surface maturation, a keratohyaline granular layer, or keratin formation; focal tissue dehiscence results in pseudopapillary architecture

Adjacent piloid gliosis may be a diagnostic pitfall

ΔΔ Differential Diagnosis—Craniopharyngioma (Small Biopsy Samples)

Epidermoid cyst

Germinoma

Rathke cleft cyst with squamous metaplasia

Pilocytic astrocytoma or other low-grade glial neoplasm (piloid gliosis)

PITUICYTOMA, SPINDLE CELL ONCOCYTOMA, AND GRANULAR CELL TUMOR OF NEUROHYPOPHYSIS

INTRODUCTION

These 3 WHO grade I tumors are derivatives of posterior gland pituicytes, and as such, are TTF-1 immunoreactive. Overall, they are rare, and may present incidentally, at autopsy or in association with other endocrine neoplasms or hemorrhage. Granular cell tumor (GCT) most commonly is noted as an incidental finding.

GROSS FEATURES

Neuroimaging features are similar to pituitary adenoma.

MICROSCOPIC FEATURES

Pituitcytoma is a spindle cell neoplasm, with plump cells in a fascicular architecture (**Fig. 13**). Mitoses are rare. Considered a mitochondria-rich variant of pituicytoma, spindle cell oncocytoma shows more epithelioid morphology, more evident nuclear pleomorphism (**Fig. 14**), and at times a lymphocytic infiltrate. Similarly, GCT may be considered as a lysosomal-rich variant of pituicytoma and resembles GCT in other anatomic locations.

DIFFERENTIAL DIAGNOSIS

Meningioma may seem similar to pituicytoma, but the latter lacks characteristic features such as whorls and calcification.

DIAGNOSIS

Pituicytoma is positive for S100 and TTF-1, with variable reactivity for GFAP.

PROGNOSIS

Surgery is the only curative option; recurrence and complications are common.[67]

Pathologic Key Features—Tumors of the Posterior Pituitary

TTF1-positive tumors considered to be related by cell of origin (posterior pituicytes)

Pituicytoma: spindle cells

Spindle cell oncocytoma: mitochondrial-rich variant; more epithelioid morphology

Granular cell tumor: lysosomal-rich variant; similar to GCT in other locations

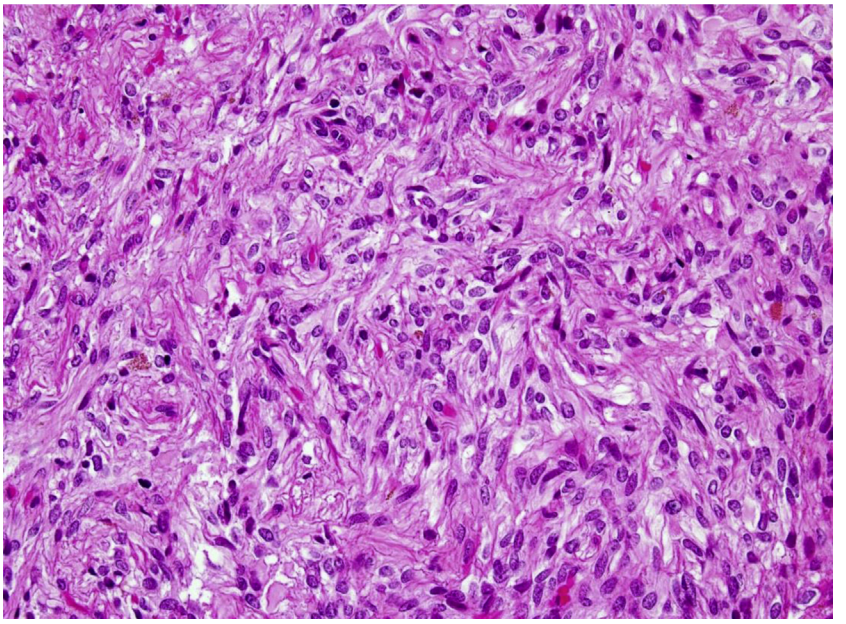

Fig. 13. Pituicytoma with spindled cells arranged in a fascicular arrangement with paucity of mitotic activity and pleomorphism.

ΔΔ *Differential Diagnosis—Tumors of the Posterior Pituitary*

Metastasis

Schwannoma

METASTASES

INTRODUCTION

Although metastases to the pituitary (MP) are overall rare (~1% in surgical series of transsphenoidal surgery for sellar lesions, ~5% in autopsy for systemic cancers, and 17% in autopsy for breast cancer in particular), rates are increasing, presumably due to improved patient survival.[68] Breast and lung carcinomas are the most common malignancies to metastasize to the sellar region. Almost always, MP are part of widespread metastases, involving at least 5 other sites (often osseous), affecting patients in the sixth to seventh decades. Occasionally, MP are the first presentation of an occult tumor, and they can also occur in young adulthood.

Clinically, MP most often present with diabetes insipidus, reflecting a predilection to involve the posterior pituitary.[68] Anterior pituitary and cranial nerve deficits may occur as well, however. Hyperprolactinemia resulting from "stalk effect" has also been described.

GROSS FEATURES

When radiographically detectable, MP show similar features to primary sellar tumors, particularly pituitary adenoma.[68]

MICROSCOPIC FEATURES

Metastatic malignancies will reflect their primary origin but on small, crushed samples, can be difficult to distinguish from a primary sellar tumor.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis often depends on the morphologic appearance of the primary, but pituitary adenoma can often enter the differential of a metastatic tumor.

DIAGNOSIS

Diagnosis is based on a combination of clinical, radiologic, histomorphologic, and immunohistochemical features, perhaps with ancillary molecular or cytogenetic testing. Preoperative diagnosis of MP is difficult. CSF cytology from lumbar puncture may be useful when meningeal spread is present. The consideration of metastasis is crucial when evaluating a patient with a sellar tumor. The clinical presentation of diabetes insipidus can strongly suggest metastases over pituitary adenoma.[68]

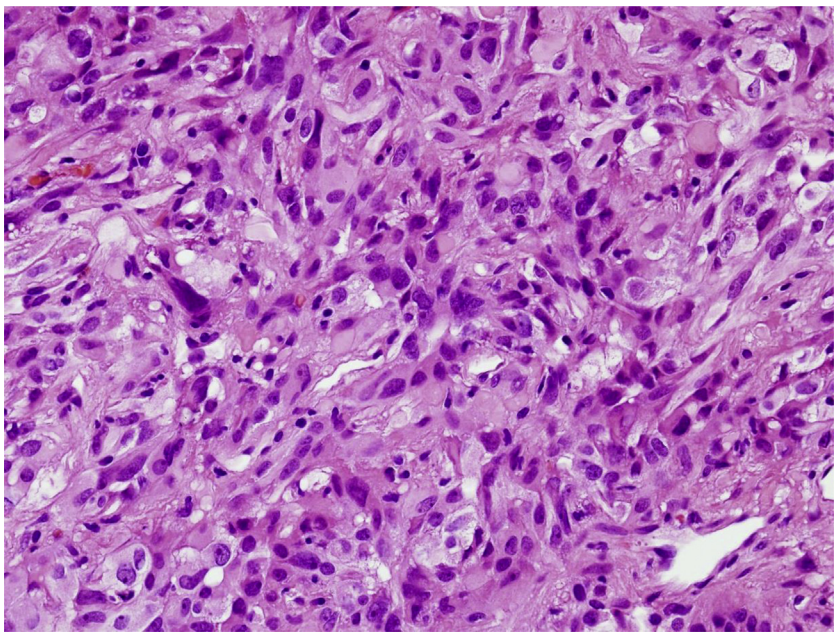

Fig. 14. Spindle cell oncocytoma with epithelioid to spindled cells in a vague fascicular architecture. Note the atypia. However, it is generally not accompanied by increased mitotic activity.

PROGNOSIS

Prognosis will depend on the treatment of the primary, metastatic burden, and patient comorbidities.

SCHWANNOMA

INTRODUCTION

Schwannomas mostly originate from peripheral, often sensory nerves such as vestibular or trigeminal and account for 8% to 10% of all primary intracranial tumors. They are uncommon in the sellar region. The origin of primary schwannomas in the sellar region is still unclear. As the sellar region has no obvious nerve, it has been hypothesized that tumors originate from lateral sellar nerve plexus, perivascular schwann cells adjacent to the medial wall of the pituitary fossa, or sensory nerves of the dura.[69] Less than 30 cases of intrasellar schwannoma have been reported in the literature.[70] The clinical presentation is related to mass effect and compression of adjacent structures. Symptoms are similar to those caused by pituitary adenomas. Suprasellar expansion may cause visual disturbances.

GROSS FEATURES

As other sellar and suprasellar lesions, MRI is the modality of choice for imaging schwannomas. However, the imaging features overlap with pituitary adenoma. On T1-weighted sequences, schwannoma is isointense or hypointense compared with gray matter and shows homogeneous enhancement with contrast. On T2-weighted images, schwannomas are more likely hyperintense than pituitary adenoma. Diffusion-weighted imaging and apparent diffusion coefficient maps show higher values with firm or fibrous tumors. Computed tomography may help show bony destruction and bony anatomy relevant for surgical planning.

Generally, schwannomas are circumscribed and may show a pseudocapsule. In the sellar region, almost all of reported tumors are firm and hypervascular.[71]

MICROSCOPIC FEATURES

Histologically, schwannomas are spindle-cell neoplasms with relatively minimal pleomorphism. Hyper- and hypocellular areas (Antoni A and B, respectively) and Verocay bodies are characteristic features. Occasional profound nuclear enlargement and atypia may be seen ("degenerative" or "ancient" change). Thick-walled blood vessels are also common.

DIFFERENTIAL DIAGNOSIS

Other spindle cell neoplasms may mimic schwannoma, including fibrous meningioma and pituicytoma. Schwannomas typically show intense reaction with S-100, collagen IV, and vimentin but are negative for EMA and glial fibrillary acidic protein (GFAP). In contrast, fibroblastic meningiomas are only moderately reactive to S-100, and pituicytomas are immunopositive for GFAP.

DIAGNOSIS

Diagnosis is made on histologic, immunohistochemical features in combination with the appropriate imaging and clinical scenarios.

PROGNOSIS

Schwannoma is a WHO grade I tumor, with surgical resection as the recommended treatment strategy.

Pathologic Key Features—Schwannoma

Spindle cell neoplasm with hyper and hypocellular areas, degenerative nuclear atypia, thick-walled blood vessels

Diffusely S100-positive; collagen IV highlights basement membrane element

Firm, hypervascular tumors

CHORDOMA

INTRODUCTION

Chordoma is a rare neoplasm considered to be of low to intermediate malignancy. It originates from notochord remnants and almost always occurs in a midline location. They are rare, representing less than 0.1% of all skull base tumors.[72] Among all chordomas, ~25% to 36% of the tumors are found in the skull base.[73] Strictly intrasellar chordomas are rare; sellar invasion is associated with clival tumors.[74]

GROSS FEATURES

By MRI, chordomas are usually hypointense on T1-weighted and hyperintense on T2-weighted images. There is a moderate to marked contrast enhancement. Because chordomas have lower

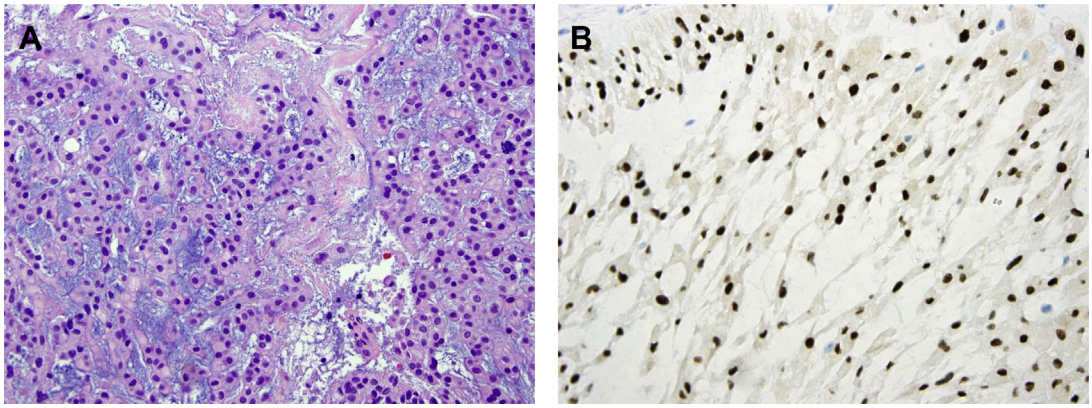

Fig. 15. Chordoma with tumor cells displaying only modest atypia, arranged in a "chordoid" pattern within a background of myxoid stroma (*A*). Physaliferous cells (multivacuolated "bubbly" cytoplasm) are seen often, albeit variably, present and are characteristic. Brachyury expression conforms to its notochordal lineage and is a consistent finding (*B*; diffuse nuclear positivity).

apparent diffusion coefficient (ADC) values, ADC can be useful to differentiate chordoma from chondrosarcoma.[75] On noncontrast CT, chordoma typically appears as well-circumscribed, hypoattenuating, heterogeneous lesion with extensive lytic bone destruction.[76]

Grossly, the tumor is a lobulated mass with a gelatinous or chondroid cut surface. When centered in bone, the tumor typically extends beyond the cortex into the surrounding soft tissue.[77]

MICROSCOPIC FEATURES

By definition, chordoma is a malignant (notochordal) tumor. The 2013 WHO classification splits chordomas into well-differentiated (classical myxoid, chondroid or mixed types) and dedifferentiated variants. The characteristic feature is vacuolated physaliferous cells, surrounded by a myxoid matrix, and arranged in a "chordoid pattern" (**Fig. 15**A). Brachyury expression (**Fig. 15**B), as well as lack of *IDH* 1 or 2 mutations, helps differentiate chordoma from chondrosarcoma.[78]

DIFFERENTIAL DIAGNOSIS

In the sellar region, the differential includes chondrosarcoma, metastatic carcinoma, and possibly, myoepithelial tumors extending from a head and neck primary.

DIAGNOSIS

A combination of imaging and microscopic features, as well as demonstration of brachyury expression, is diagnostic of chordoma.

PROGNOSIS

Chordoma is known to have aggressive local behavior and a high rate of recurrence. Metastasis may also occur; its long-term prognosis is poor. Resection using an endonasal endoscopic approach is recommended for skull base chordomas. However, because of their location and extension, radical resection is not always achievable. In addition, although an aggressive or radical resection approach has been suggested to be likely the most important factor influencing chordoma relapse and long-term patient survival, there is still no agreement on the standardized classification for the extent of tumor excision.[79] Proton beam therapy is increasingly recommended for chordomas.[80] Medical therapy options for recurrence include imatinib and sorafenib as palliative treatment options to slow disease progression or alleviate symptoms. In addition, several case reports have noted activity of sunitinib and epidermal growth factor receptor inhibitors (cetuximab, erlotinib, gefitinib).

Pathologic Key Features—Chordoma

Pathognomonic feature is the presence of physaliferous cells and attempts to form the notochord; positive for the transcription factor brachyury

WHO 2013 classification specifies well-differentiated (classical myxoid, chondroid or mixed types) and dedifferentiated variants

ΔΔ Differential Diagnosis—Chordoma

Low-grade chondrosarcoma

Metastatic carcinoma or myoepithelial neoplasm with direct extension from head and neck primary

Chondroma

Metaplastic meningioma

ATYPICAL TERATOID/RHABDOID TUMORS IN ADULTS

INTRODUCTION

Atypical teratoid/rhabdoid tumor (AT/RT), an embryonal, primary central nervous system (CNS) malignancy defined by the 2016 WHO by loss of INI1 (alterations in *SMARCB1* gene) or BRG1 (alterations in *SMARC4A* gene) protein expression and often composed partly by "rhabdoid" cells, most commonly occurs in children younger than 3 years. However, several cases have now been described in adults, both in the sellar region (~46% of 50 cases identified in adults) and elsewhere in the neuraxis.[81]

GROSS FEATURES

On MRI, AT/RTs are isodense to hyperintense on FLAIR images and show restricted diffusion. Most tumors are variably contrast enhancing. Leptomeningeal dissemination at presentation is less commonly reported in adults (4%) as opposed to the pediatric population (~25%). Grossly, the tissue is similar to medulloblastoma and is soft, pinkish-red, demarcated from adjacent parenchyma, and necrotic with hemorrhage.

MICROSCOPIC FEATURES

AT/RTs are variegated, primitive-appearing tumors. The definitive feature is a population of rhabdoid cells, characterized by eccentric nuclei containing vesicular chromatin, prominent eosinophilic nucleoli, abundant cytoplasm, and eosinophilic globular cytoplasmic inclusions. Usually, this is a minor population. Other components of the tumor include primitive neuroectodermal, mesenchymal, and epithelial, with the small-cell neuroectodermal component being most frequent among these.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes any primitive-appearing malignancy, including metastases.

DIAGNOSIS

Diagnosis is based on the loss of INI1 or BRG1 proteins by immunohistochemistry or by demonstration of alterations in *SMARCB1* or *SMARC4A* genes. Other immunostains may be useful, including EMA, SMA, and vimentin in rhabdoid cells; GFAP, neurofilament protein, and synaptophysin are also commonly expressed. Germ cell markers and skeletal muscle markers are not typically expressed.

PROGNOSIS

Given the limited number of AT/RT cases in adults, overall prognosis and impact of extent of resection and adjuvant therapy remains unclear. Of 50 patients, 31 (62%) died, with an average time to death of 20 months (0–168 months). Of 28 patients who received combined radiotherapy and chemotherapy, 15 were alive at follow-up, ranging from 6 months to 17 years. Time to death for the remaining 13 of these 28 ranged from 3 months to 3 years after diagnosis. There was no statistically significant difference in outcome for patients with and without gross total resection.[81]

Pathologic Key Features—Atypical Teratoid/Rhabdoid Tumor in Adults

Primitive, high-grade malignancy rarely found in adults

Alterations of the *SMARCB1* or *SMARC4A* genes (loss of INI1 or BRG1 protein respectively)

Rhabdoid cells are a rare but defining feature

Primitive neuroectodermal (predominant), mesenchymal, and epithelial components

ΔΔ Differential Diagnosis—Atypical Teratoid/Rhabdoid Tumor in Adults

Metastatic poorly differentiated malignancy

Malignant germ cell tumor

High-grade lymphoma

Other high-grade primary CNS neoplasm with embryonal features

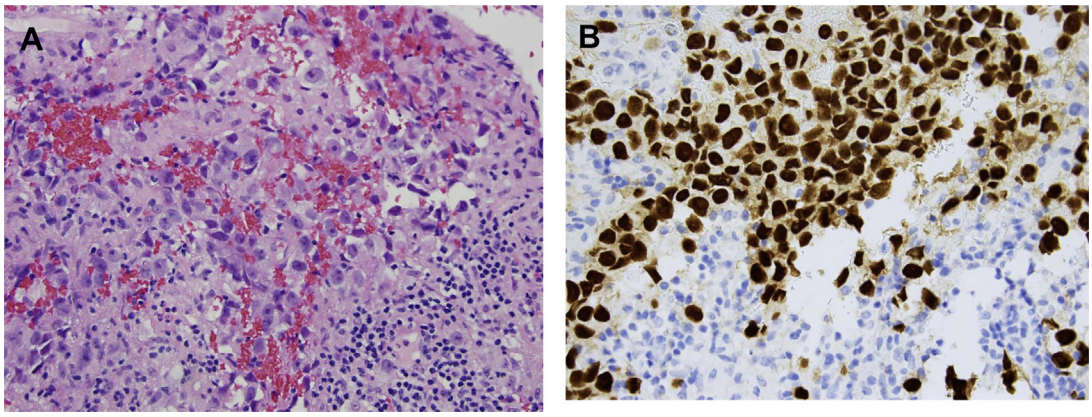

Fig. 16. Germinoma. As elsewhere, germinoma is composed of dual cell population. Although the neoplastic cells are large with pale eosinophilic to vacuolated cytoplasm with vesicular nuclei and prominent nucleoli, the intermixed lymphocytes are nonneoplastic (*A*). Sometimes they can be associated with significant granulomatous inflammation, which can be a diagnostic pitfall on small biopsies. Diffuse and strong nuclear expression of OCT3/4 within tumor cells is diagnostic (*B*).

OTHER TUMORS MAY OCCUR IN THE SELLAR REGION

As a final note, other tumors may present in the sellar region, including germ cell tumors (**Fig. 16**), diffuse midline glioma defined by H3 K27M mutation, optic pathway glioma, chondrosarcoma, lipoma, meningioma, paraganglioma, gangliocytoma, hemangioblastoma, solitary fibrous tumor/hemangiopericytoma, hematopoietic neoplasms including Langerhans cell histiocytosis (**Fig. 17**) as well as plasma cell neoplasms, melanomas, and metastases have all been described. The histopathologic features of these tumors are characteristic and not unique to this location. Local extension from a nasal, sinonasal, or nasopharyngeal malignancy is also not infrequent (**Fig. 18**).

DISCLOSURE

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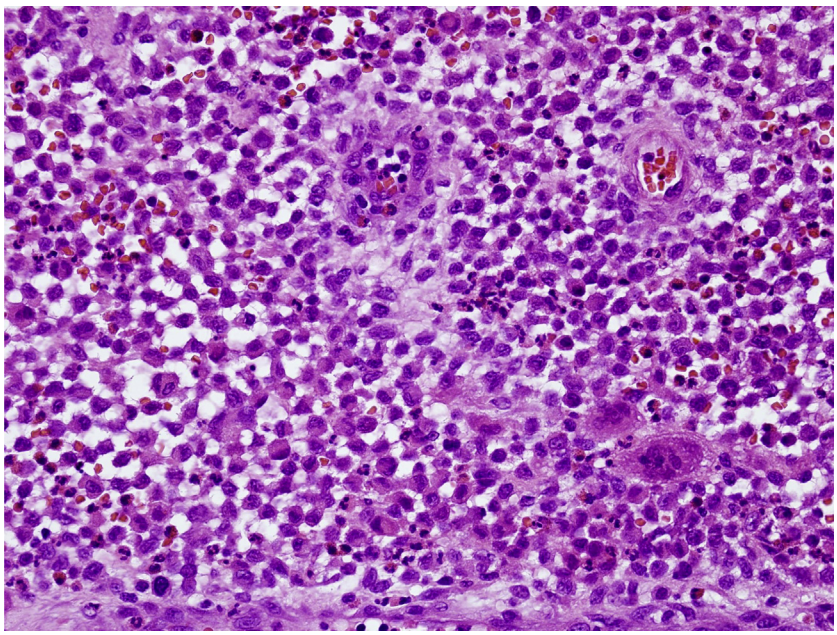

Fig. 17. Langerhan cell histiocytosis with sheets of histiocytic cells containing nuclear groves and scattered multinucleate giant cells harboring similar nuclear features. Eosinophils may not always be prominent and can be only focally present or lacking. Strong immunoreactivity with CD1a is a consistent feature.

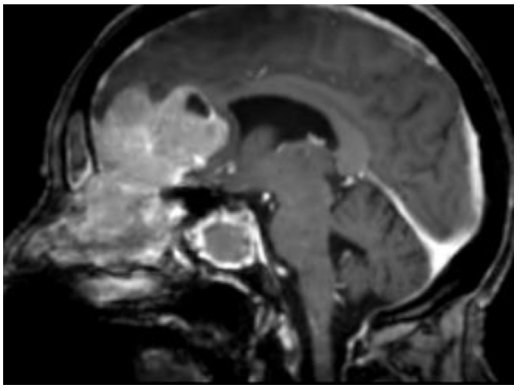

Fig. 18. **Local invasion from a surrounding nasal/paranasal malignancy is not uncommon. MRI from a patient with olfactory neuroblastoma demonstrating marked intracranial extension with involvement of the sella and brain.**

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