Diagnostic Controversies in Pituitary Tumor Pathology

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INTRODUCTION

Tumors of the pituitary gland and sellar region represent approximately 10–15% of all brain tumors [1]. Numerous types of tumors may involve the sellar region, reflecting its complex anatomy. Table 1 lists the most frequent tumors arising in the sellar and parasellar region. The most common tumors are, by far, the pituitary adenomas, benign epithelial tumors derived from cells of the adenohypophysis. In fact, pituitary adenomas represent the third most common primary intracranial tumor in neurosurgical practice, outnumbered only by gliomas and meningiomas [1]. Pituitary adenomas predominantly affect females between the third and sixth decades; however, no age group is spared [1]. Adenomas are uncommon in the pediatric population, but most tumors of childhood are clinically functioning adenomas and thought to be more aggressive [2]. Rates for pituitary tumors in the USA are slightly higher among blacks than whites [1]. Incidental adenomas can be found in nearly 10% of autopsied patients [3, 4].

Comparatively, primary tumors of the neurohypophysis are rare and in general are similar to primary tumors of the central nervous system. The neurohypophysis, however, is a common site for metastases [5].

In addition to tumors, a variety of non-neoplastic lesions may affect the pituitary gland, bringing a number of processes into the differential diagnosis of tumors involving this region.
TABLE 1 – Tumors and Tumor-Like Lesions of the Pituitary Gland and Sellar Region

| TUMORS OF THE ANTERIOR PITUITARY            | - Pituitary Adenoma  
|                                            | - Atypical Adenoma  
|                                            | - Pituitary Carcinoma  
|                                            | - Spindle Cell Oncocytoma  
| TUMORS OF THE POSTERIOR PITUITARY          | - Pituicytoma  
|                                            | - Gangliocytoma  
|                                            | - Granular Cell Tumor  
| TUMOR OF NON-PITUITARY ORIGIN              | - Craniopharyngioma  
|                                            | - Meningioma  
|                                            | - Chordoma  
|                                            | - Langerhans Cell Histiocytosis  
|                                            | - Metastases  
| CYSTIC LESIONS                             | - Rathke’s Cleft Cyst  
|                                            | - Arachnoid Cyst  
|                                            | - Epidermoid/Dermoid Cyst  
| INFLAMMATORY LESIONS                       | - Lymphocytic Hypophysitis  
|                                            | - Granulomatous Hypophysitis  
|                                            | - Sarcoidosis  

TUMORS OF THE ANTERIOR PITUITARY GLAND

Pituitary Adenomas

1. Classification

Pituitary adenomas are classified clinically into two main groups: the clinically functioning adenomas and the clinically non-functioning adenomas, according to whether or not an endocrine syndrome is present. Most adenomas are functioning tumors and include PRL-
producing, GH-producing, ACTH-producing, and TSH-producing adenomas [6]. However, about a third of all pituitary adenomas are unassociated with either clinical or biochemical evidence of hormone excess [7]. In this group are included the gonadotroph-adenomas that produce FSH and LH, the less differentiated null-cell adenomas, and the silent adenomas. These clinically non-functioning adenomas commonly present with symptoms related to local mass effect such as headaches, neurologic deficits in the cranial nerves including visual field disturbances, and mild hyperprolactinemia due to pituitary stalk compression (the so-called stalk effect).

According to tumor size and gross anatomic features, adenomas are divided into microadenomas (tumors < 1cm in diameter) and macroadenomas (tumors ≥ 1cm in diameter). Giant adenomas (tumors > 4cm) rarely occur. Macroadenomas show an increased tendency toward suprasellar extension, gross invasion, and recurrence. A radiologic classification proposed by Hardy [8], is the most used in clinical practice.

A number of attempts to histologically classify pituitary adenomas have been made over the years. From the first morphologic classification proposed by Cushing in 1912 to the present time, pituitary adenomas classifications have aimed to combine the tumor morphologic aspects with the clinico-endocrinologic presentation of the patients. The recommended World Health Organization (WHO) classification from 2004 [9], which is now used by most laboratories, incorporates the clinical and radiological presentation of the tumor with its morphologic features, immunohistochemical profile, and ultrastructural appearance (Table 2). This classification has helped not just to understand further the cytogenesis of pituitary adenomas, but also to identify different tumor types that may present clinically with similar symptomatology.
**TABLE 2 - Morpho-Functional Classification of Pituitary Adenomas**

<table>
<thead>
<tr>
<th><strong>CLINICAL PRESENTATION</strong></th>
<th><strong>ADENOMA SUBTYING</strong></th>
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<tbody>
<tr>
<td>PRL-secreting adenomas</td>
<td>Sparsely-granulated Lactotroph Adenoma</td>
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<tr>
<td></td>
<td>Densely-granulated Lactotroph Adenoma</td>
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<td></td>
<td>Acidophilic stem cell Adenoma</td>
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<tr>
<td>GH-secreting adenomas</td>
<td>Densely-granulated Somatotroph Adenoma</td>
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<td></td>
<td>Sparsely-granulated Somatotroph Adenoma</td>
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<td>GH- and PRL-secreting adenomas</td>
<td>Mixed Somatotroph-Lactotroph Adenoma</td>
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<td>Mammosomatotroph cell Adenoma</td>
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<td>ACTH-secreting adenomas</td>
<td>Corticotroph Adenoma</td>
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<td>TSH-secreting adenomas</td>
<td>Thyrotroph Adenoma</td>
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<td>Gonadotropin-secreting adenomas</td>
<td>Gonadotroph Adenoma</td>
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<tr>
<td>Non-functioning adenomas</td>
<td>Null-cell Adenoma</td>
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<td></td>
<td>Oncocytoma</td>
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<tr>
<td>Silent adenomas</td>
<td>Silent Corticotroph Adenomas (subtypes 1 and 2)</td>
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<td></td>
<td>Silent Adenoma subtype 3</td>
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Pituitary adenomas are classified according to the hormone content of the tumor cells as assessed by immunohistochemical stains. The immunohistochemical classification provides significant information for clinical practice [10]. However, immunohistochemistry alone does
not discriminate a number of specific subtypes of tumors which have prognostic clinical significance and, in these instances, analysis of the ultrastructure of adenomas is necessary [11].

The WHO classification employs updated lineage studies that result in new and appropriate clustering of a variety of tumor subtypes. This has changed our understanding not only of the pathogenesis of these tumors but also opens new avenues of pharmacological treatment, which hopefully will result in increasing levels of hormonal control. Additionally, potentially useful data with regard to oncogenes and the loss of tumor suppressor genes as pathogenic mechanisms for these tumors are provided, and continue to accumulate based on molecular biology studies, which extend to signal transduction processes and to the influence of a variety of transcription factors.

A few highlights of the new WHO classification include enhanced evidence that many of the non-secreting tumors that were formally classified as “null cell” tumors are actually derived from the gonadotroph family. There is continuing evidence that morphological features, including ultrastructure, e.g., the sparsely granulated growth hormone adenoma, the mammosomatotroph adenoma, the acidophil stem cell tumor and a variety of silent subtypes, may correlate with aggressive tumor behavior.

2. Grading

Perhaps the most controversial aspect of the new WHO classification is the introduction of a grading system for pituitary endocrine tumors. These tumors are now categorized in typical adenoma (8272/0), atypical adenoma (8272/1), and pituitary carcinoma (8272/3).
The majority of pituitary adenomas are typical with bland histological features, infrequent mitotic figures, and a Ki-67 proliferative index less than 3%. The designation of *atypical adenoma* is reserved for tumors that show histological features suggestive of aggressive clinical behavior. These adenomas are characterized by “atypical morphologic features suggestive of aggressive behavior such as invasive growth” [12]. In addition, other features seen in these tumors include elevated mitotic index, a Ki-67 labeling index greater than 3%, and extensive nuclear staining for the p53 protein by immunohistochemistry [12]. Close follow-up of patients with atypical adenomas is recommended.

Pituitary carcinomas are very rare, comprising less than 1% of all pituitary neoplasms [12-14]. By definition, pituitary carcinomas are characterized by demonstration of either craniospinal dissemination or systemic metastases [12]. The majority of cases are endocrinologically functioning tumors; the most common are PRL-secreting tumors, followed by ACTH-secreting [13, 14]. Non-functioning carcinomas constitute about 15-20% of the cases including gonadotroph, silent corticotroph, and rarely null cell carcinomas [13, 14].

There are no morphologic criteria to distinguish locally aggressive or even markedly atypical adenomas from carcinomas when the tumor is confined to the sella turcica. Standard morphologic features associated with malignancy including hypercellularity, nuclear and cellular pleomorphism, increased mitotic activity, necrosis, and dural/bony invasion are commonly present but are not necessarily diagnostic of carcinoma. Ki-67 labeling indices are quite variable and show considerable overlap with ordinary pituitary adenomas. However, they are often higher in metastatic deposits. Additionally, unlike pituitary adenomas, carcinomas appear to show overexpression of the p53 protein by immunohistochemistry [13].
3. Invasiveness and proliferative potential of pituitary adenomas

Pituitary adenomas either grow expansively or invade adjacent structures. In the first case, the tumors are usually small, well demarcated, and restricted to the sella turcica. Invasive adenomas usually have a more rapid growth rate, spreading into neighboring tissues such as the sphenoid sinus, the cavernous sinus and, in some cases, the brain [15, 16].

The mechanisms of progression of pituitary adenomas to more aggressive, invasive tumors are not yet totally understood. A proliferative continuum from benign adenoma to invasive adenoma and carcinoma has not been demonstrated in the great majority of tumors. The propensity of pituitary adenomas to infiltrate locally and invade adjacent structures appears to be independent of the histologic features of the tumors. Invasive adenomas do not necessarily show histologic features of tumor aggressiveness, including pleomorphism, nuclear atypia, and mitotic activity, as seen in atypical adenomas. Although both clinically functioning and non-functioning adenomas may present as invasive tumors, gross invasion appears to be more frequent in functioning tumors [15, 16]. On the other hand, there is an apparent relationship between invasiveness and tumor size in that macroadenomas have a higher frequency of invasion than microadenomas [15].

Studies of proliferative potential of pituitary adenomas have been applied as an adjuvant tool for distinguishing aggressive pituitary adenomas from the most common benign tumors [17]. These studies have revealed that the majority of tumors show a low growth fraction, with most Ki-67 indices being less than 3%. The mean growth fractions are significantly higher among invasive adenomas and pituitary carcinomas when compared with non-invasive
adenomas [17, 18]. Although these data may suggest that a significant correlation exists between Ki-67 labeling index and pituitary tumor invasiveness, a significant correlation between proliferative index and tumor recurrence has not yet been demonstrated [18].

Conclusions

One of the most important prognostic features of pituitary adenomas remains their hormonal profile and pathological subtype classification. It appears that the recognition of specific subtypes of adenomas that have a higher propensity for aggressive clinical behavior, including the sparsely granulated growth hormone adenoma, the densely granulated lactotroph adenoma, the silent type 3 adenoma and the silent corticotroph adenoma, in a systematic grading designation may assist in clinical management and understanding of the epidemiology of these tumors.

Nevertheless, there remain a number of areas of controversy with regard to the classification of pituitary tumors. Controversy exists with regard to the phenomenon of invasion of tissues surrounding the tumor, including the brain, the cavernous sinuses and the skull base. Although some studies have shown that invasion in and of itself did not correlate with recurrence or with poor outcome, it is a fact that most of the patients who die from pituitary tumors have invasive adenomas.
References


Update on primary non-adenomatous sellar region masses: hypophysitis, pituicytoma, spindle cell oncocytoma, craniopharyngioma

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HYPOPHYSITIS

Hypophysitis is an uncommon disorder involving the pituitary gland which, by definition, shows inflammatory cells within the gland or nearby infundibular stalk. It is not a singular disease, but rather several very different entities and is rare when put in the context of all sellar region masses, occurring as <1% occurrence of pituitary surgical cases. Secondary and primary types have been recognized, and, within the primary type, cases are further subclassified based on the type of inflammatory cell(s) that are present.

Secondary hypophysitis by definition are examples where an underlying systemic inflammatory condition or tumor is co-associated with the inflammation in the gland. In contrast, primary hypophysitis is devoid of known co-associated condition and considered an autoimmune disorder or the gland.

Before making the diagnosis of inflammation in the pituitary gland, either at biopsy or autopsy, several points should be mentioned:

1. lymphocytes are not normally present in the anterior pituitary gland; significant numbers of inflammatory cells in pituitary gland is always a pathological condition.

2. pituitary adenomas, the most frequent mass lesion encountered in the sellar region, like normal anterior gland, do not routinely contain significant lymphocytic infiltrates.
**Major points regarding hypophysitis include:**

3. hypophysitis presents as a mass lesion of the pituitary gland which simulates a non-secretory pituitary adenoma by clinical and neuroimaging studies. Preoperative diagnosis is difficult; in a significant percentage of cases, the diagnosis of hypophysitis is completely unsuspected clinically and comes only at the time of histological examination of the tissues by the pathologist.

4. if the diagnosis can be recognized at the time of intraoperative frozen section consultation, surgical treatment may be altered in cases of pure (primary) hypophysitis without a co-existent tumor or cyst. In cases of pure hypophysitis, neurosurgical treatment might include a smaller decompressive procedure or even biopsy alone. Aggressive resection of the mass, as would be indicated for a pituitary adenoma, ideally is avoided in cases of primary hypophysitis.

5. diagnosis of lymphocytes or other types of inflammatory cells in the gland should be made only after excluding crushed, compressed normal anterior pituicytes. Less commonly, diagnostic dilemmas are posed by prolactinomas that have been treated preoperatively with dopamine agonists such as bromocriptine or cabergoline or cases of apoplexy.

6. **Workup should include**

reticulin, CD45 (leukocyte common antigen), CD3 (T cells), CD20 (B cells), CD68 (macrophages), and CD138 (plasma cells), panel of anterior pituitary hormones to rule in/out co-existent pituitary adenoma.

Infectious causes of hypophysitis very rare; special stains for organisms are only indicated in rare examples.

7. **Rule in/out secondary hypophysitis:** those cases in which an inciting infectious agent, systemic inflammatory disease, or co-associated sellar region tumor or cyst can be identified. Correlation
with serology and systemic organ findings is often necessary to render a correct diagnosis in these instances of secondary hypophysitis. This usually involves consulting the medical record, laboratory data, and/or the clinical care team of the patient. Sarcoidosis, Wegener granulomatosis, Sjögren disease are considerations.

8. In select hosts, such as pediatric patients, **have a high index of suspicion for Langerhans cell histiocytosis, non-Langerhans cell histiocytosis, or germ cell tumor** of the sellar-suprasellar region and use immunohistochemical stains. Lymphoma of sellar region occurs but is rare.

9. Secondary hypophysitis associated with Rathke cleft cysts, craniopharyngiomas, pituitary adenomas have been reported; look for these histological features.

10. **If all of the above are excluded, case is primary hypophysitis by definition.**

11. **Primary hypophysitis** was originally thought to be almost exclusively in young women during late pregnancy or in the early postpartum period, especially the third trimester. However, in the last 20 years of primary hypophysitis, studies have shown only 20-30% were associated with pregnancy or the postpartum period. In addition, only 25-30% were co-associated with other autoimmune clinical conditions. In some reports, males and females were found to be nearly equally affected.

12. Primary hypophysitis is most commonly divided into **lymphocytic, granulomatous, and xanthomatous** types with some workers additionally recognizing mixed **xanthogranulomatous** and **necrotizing** forms. Lymphocytic hypophysitis is the most frequent subtype of primary hypophysitis currently encountered by pathologists, followed by granulomatous.

13. Xanthomatous hypophysitis is the rarest of the three types of primary hypophysitis and may be the most different amongst these three subtypes of primary hypophysitis. Gutenberg et al. found that lymphocytic hypophysitis -- but not granulomatous or xanthomatous types of hypophysitis --
occurred in association with pregnancy or autoimmune diseases. Some clinical studies show that lymphocytic and granulomatous hypophysitis more often resulted in severe dysfunction of the endocrine axes (particularly adrenal, gonadal and thyroid), than did cases of xanthomatous hypophysitis.

Several groups have found that Rathke cleft cyst can be associated with several types of hypophysitis, including xanthogranulomatous or xanthomatous.

14. Clinically, most patients with primary hypophysitis of whatever histological subtype present with headache, hypopituitarism, and suprasellar mass that may compromise vision. Diabetes insipidus, thickening of the pituitary stalk, or enlargement of the posterior gland point is seen in the subset of hypophysitis which involves infundibular stalk and/or posterior gland.

15. no preoperative laboratory test for hypophysitis exists. Antipituitary antibodies have been reported in patients with a variety of different conditions and these antibody tests are not widely available.

16. If the diagnosis of primary hypophysitis is suspected preoperatively, and if vision is not being compromised by severe chiasmal compression, attempts may be made to manage the patient medically. Treatment is often with anti-inflammatory drugs such as high-dose methylprednisolone or dexamethasone (with or without successful outcome). Azathioprine, rituximab have been tried. Hormonal replacement is usually necessary. Partial hypophysectomy may still be required for decompression of the mass. Stereotactic radiation is an additional treatment modality.

17. The latest updates on hypophysitis are 1.) the identification of a novel clinical entity, IgG4-related disease, and its hypophysitis component, and 2.) the emergence of hypophysitis related to
treatment of metastatic melanoma or other cancers with the monoclonal immunomodulatory antibody directed against cytotoxic T-lymphocyte antigen 4 (CTLA4) such as ipilimumab.

18. IgG4-related disease shows elevated serum IgG4 concentrations and tissue infiltrates by IgG4-positive plasma cells. Many organs can be affected by IgG4-related disease. **Plasma cell hypophysitis** represents yet another histological subtype of hypophysitis in addition to lymphocytic, granulomatous, xanthogranulomatous, and mixed xanthogranulomatous and necrotizing forms.

19. Hypophysitis has been now associated with administration of immunomodulatory drugs: -interferon alpha and ribavirin

**-CTLA-4 blocking antibodies** (ipilimumab): occurs in 4.9-17% of patients using the drug. Hypopituitarism develops at a median time of 11 weeks after starting drug; occurrence is unrelated to the underlying type of cancer. Patients present with headache, fatigue, lethargy, nausea and loss of libido, but only very rarely with visual field defects since the enlargement of the pituitary gland is usually modest. This contrasts the condition with primary hypophysitis, where visual disturbance and optic chiasmal compression uncontrolled by steroids is the main indication for surgical debulking. Treatment is surveillance and high-dose glucocorticoids. Juszczak et al. note that "in all reported cases of ipilimumab-induced hypophysitis, symptoms resolved with glucocorticoids, T4 and testosterone replacement". Hence, the condition should rarely come to surgical debulking in the future and is unlikely to present itself as a surgical specimen for the pathologist.

**REFERENCES:**


PITUICYTOMA

Pituicytoma was first codified in the 2007 edition of the World Health Organization (WHO).

Pituicytoma is an uncommon mimic of non-secretory pituitary adenoma that occurs in region of the neurohypophysis and infundibular stalk, with approximately 55 reported cases.

1. Preoperative confident diagnosis of pituicytoma versus other sellar region masses such as non-secretory pituitary adenoma, spindle cell oncocytoma, granular cell tumor, or even some meningiomas is difficult to impossible, based on overlapping clinical presentation, endocrine features, or neuroimaging characteristics.

2. Pituicytoma patients present clinically with symptoms referable to mass effect, with compression of the optic chiasm and pituitary gland resulting in headache, visual disturbance and hypopituitarism.

3. Some are purely intrasellar but many are also suprasellar or mixed. By neuroimaging, up to 25% of pituicytomas are separate from the pituitary gland, but the remainder appeared infiltrative of the underlying pituitary gland. Most are solid and homogeneously enhance.
4. A significant subset of pituicytomas appears to be extremely vascular. Some have bled excessively during surgery and one presented with spontaneous hemorrhage.

5. Pituicytomas are slowly growing, usually treated by surgical resection alone, and were assigned a WHO grade of I in 2007. Subtotal resection was noted to be potentially associated with slow recurrence, but no metastases or malignant transformation have been reported.

6. Pituicytomas are histologically composed of solid sheets of elongate bipolar spindle cells arranged in fascicles or with storiform pattern.
- Unlike pilocytic astrocytomas, biphasic pattern, coarsely fibrillar cytoplasm, Rosenthal fibers, calcifications, and eosinophilic granular bodies are all lacking.
- Cytoplasm shows neither granularity nor PAS-positivity, as might be seen with granular cell tumor of infundibulum, and lacks vacuolization.
- Cell borders are distinct and tumors lack the hyalinized blood vessels or pericellular reticulin seen with schwannomas.
- Whorls, psammoma bodies, or nuclear features of meningiomas are lacking.

7. IHC profile shows immunostaining for
- Vimentin (nearly 100% cases)
- S-100 protein (nearly 100% of cases)
- Variability in immunoreactivity for glial fibrillary acidic protein (GFAP) (about 75%)
- Negative for markers expected in pituitary adenomas such as synaptophysin, chromogranin, or any of the anterior pituitary hormones. Negative immunostaining for synaptophysin and neurofilament (for axons) allow pituicytoma to be immunohistochemically distinguished from normal posterior pituitary gland, which could be a diagnostic consideration on small biopsies.
- **epithelial membrane antigen (EMA)** IHC also highly variable (<1/3), but when present is usually focal and cytoplasmic rather than membranous, usually allowing distinction from meningioma.

**REFERENCES**


**SPINDLE CELL ONCOCYTOMA**

Spindle cell onc cytoma was also first codified in 2007 WHO. Even with the 5 initial reported examples, only approximately 20 total cases have been published. All have occurred in adults with a mean of 56 years.

1. Clinical presentation and neuroimaging usually fails to definitively distinguish between non-secretory pituitary adenoma and spindle cell onc cytoma, or even between pituicytoma and spindle cell onc cytoma.
2. **visual disturbance** is presenting symptom in approximately 1/2 of each tumor type, although panhypopituitarism may be more typical of spindle cell oncocytoma than pituicytoma. Headache was identified in many patients with spindle cell oncocytomas, although almost none have diabetes insipidus.

3. Neuroimaging shows spindle cell oncocytomas are "infiltrating" and cannot clearly separated from the pituitary gland. All are **both suprasellar and intrasellar**, unlike the occasional pure sellar location of pituicytoma.

4. Several of the uncommon clinical and biological features seen in pituicytoma are shared with spindle cell oncocytoma, including occasional association with other endocrine abnormalities in the same patient and **tendency for bleeding or high vascularity**.

5. **Spindle cell oncocytomas** histologically are characterized by interlacing fascicles of spindled to epithelioid cells with variably oncocytic cytoplasm. Some examples show significant pleomorphism or small infiltrates of non-neoplastic inflammatory cells. The overlap with pituicytoma may be significant in some instances. Mitotic counts are usually less than 1/10 HPFs and MIB-1 rates usually less than 8%.

6. IHC profile of spindle cell oncocytoma:

   - spindle cell oncocytoma and pituicytoma share immunoreactivity for **vimentin, S-100 protein, and galectin-3**

   - negative GFAP, cytokeratins, CD34, synaptophysin, chromogranin, bcl-2, CD68, and pituitary hormones

   - **EMA is often positive**
- key distinguishing feature between spindle cell oncocytoma and pituicytoma is the finding of abundant cytoplasmic mitochondria by electron microscopy or significant immunoreactivity for antimitochondrial antibody MU213-UC

7. assigned a WHO grade of I. In some instances, long term followup has shown excellent prognosis. However, as more case reports emerge, it appears that recurrences may be even more frequent than with subtotally-resected pituicytomas.

REFERENCES

The characteristic histological features of adamantinomatous craniopharyngioma are known to all surgical pathologists and do not require review. Papillary craniopharyngioma, in contrast, composes only 10% of cases, is almost exclusively seen in adults and thus, features are not as widely known.

Papillary craniopharyngiomas by neuroimaging may show cystic, solid, or even cyst with mural nodule-like features, differing from the complex cystic/solid features seen in adamantinomatous types. On CT scans, they lack calcification. Infrequently, they are located entirely in the third ventricle, but most often they are simply suprasellar rather than intrasellar. Macroscopically, the tumor lacks dense adherence to the brain like the adamantinomatous variant of craniopharyngioma, and lacks the cholesterol-rich “machine oil” content of adamantinomatous craniopharyngioma. Microscopically, it is defined by solid sheets of well-differentiated epithelium forming papillae due to dehiscence of epithelium where it surrounds fibrovascular cores. Some whorls can be present, but no wet keratin, ghost cells, or calcification is seen. In rare examples, goblet or ciliated cells are seen, indicating possible overlap with Rathke cleft cyst.

By immunocytochemistry, these are positive for cytokeratins and epithelial membrane antigen, and are CK7-positive in all layers except the basal layer. Although distinction from Rathke cleft cyst is not usually difficult, in problematic cases, the negative immunostaining for CK8 and CK20 in papillary craniopharyngiomas has been contrasted with its positive staining in Rathke cleft cysts.
From a biological standpoint and from an immunohistochemical standpoint, the finding of beta-catenin in the nucleus in adamantinomatous craniopharyngiomas, but not in papillary craniopharyngiomas, has been one of the leading developments in the last few years.

It has become evident that although WHO classifies craniopharyngiomas as WHO grade I tumors, they do not have an overall favorable prognosis. This seems particularly true in adults, where there is significant morbidity and mortality. Although gross total resection may reduce recurrence, the hypothalamic location of most adamantinomatous craniopharyngiomas and their dense adherence to surrounding structures makes radical excision fraught with problems. Significant cognitive problems can occur after surgery.

**Malignancy in craniopharyngiomas** has been reported in the past, but this occurrence was further appreciated after the report by Rodriguez et al. in AJSP.

**REFERENCES**

Atypical Teratoid/Rhabdoid Tumor (AT/RT) in the Sellar Region

AT/RTs are rare malignant neoplasms that almost always appear in patients less than three years, often below two, or even at or less than one. A small fraction of an already rare tumor occurs in the AT/RT tumor disposition syndrome. The lesion is at least as common in the posterior fossa, e.g. cerebellopontine angle, as in the supratentorial compartment.

AT/RT is thus familiar to pediatric pathologists, neuropathologists and pathologists serving large hospitals attended by pediatric neurosurgeons. It is otherwise largely unknown. The tumor does occur in adults, albeit rarely however, with an unexplained predilection for the sellar/suprasellar region, a site where, thus far, all examples seem to have occurred woman. This age and gender favoritism is unexplained. As illustrated in the present case, such a rare, histologically undifferentiated lesion is almost certainly to be diagnostic problems, and clearly not one of the conventional regional lesions such as pituitary adenoma, craniopharyngioma, pituicytic tumor, meningioma, etc. A metastasis may be suspected.

AT/RTs assume many histological guises: 1) rhabdoid tissue with round cells with large eccentric pale nuclei with prominent nucleoli, 2) non-descript yet distinctive large pale, jumbled cells, 3) spindling populations large and dense enough to mimic medulloblastoma or supratentorial PNET. Mixed patterns are common. Most lesions are focally necrotic.

The lesion’s polyimmunophenotypic profile may come as a surprise since, aside from uncommon focal crude epithelial formations or neuroblastic rosettes, tumors are undifferentiated. Immunoreactivities, generally of individual cells or small clusters, variably for EMA, GFAP, cytokeratins, smooth muscle actin, and synatophysin. Most lesions are not positive for all markers, but manyare reactive at least for EMA, cytokeratins, and GFAP. In this context, the diagnosis wants only confirmation by loss of staining (“loss of retention”) of tumor cell nuclei for INI1. Normally stained cells in the background, whether endothelial, fibroblast, or inflammatory, are valuable internal controls. Staining of tumor cell nuclei should be interpreted as lost only in the presence of these non-neoplastic cells whose immunopositivity confirms reactivity of the tissue and appropriate execution of the staining procedure.

Pituitary Blastoma

Only six cases, some of incompletely studied, record this rare lesion that is felt to represent neoplastic transformation of embryonic adenohypophysis. In accord with the early stage thereof, the normally early-appearing ACTH is the principal hormone produced, and is released in sufficient quantity to produce Cushing disease. Other clinical expressions relate to mass effect. All patients have presented in the first year of life. There is an evolving understanding that some cases are part of Dicer1 syndrome (pleuropulmonary blastoma, cystic nephroma, etc.).

The cellular lesions are remarkable for overall high cellularity and, most distinctly, epithelia, including goblet cells in some cases, that suggest differentiation to Rathke cleft. Small blastoma cells and larger, paler secretory cells fill out the spectrum. Necrosis and high mitotic activity have been present in some, but not all cases.

Immunohistochemically, secretory cells are positive for ACTH and synaptophysin whereas epithelia are more likely to react for cytokeratins and EMA. Overlap in staining between secretory and epithelial cells may be present. Positivity for annexin-1 has been used to support the presence of differentiation to folliculostellate cells.

Electron microscopy reveals cells with features suggesting folliculostellate cells.

Outcomes have varied.

Osteolipoma of the Tuber Cinereum
This rare lesion that present variably with visual disturbances, cranial nerve signs and endocrine abnormalities. It is pea- or bean-sized shell of calcification with a lipomatous center. One or more such closely apposed lesions may be present. By CT, they are spherical or cylindrical with a hyperdense bony shell encompassing hypodense adipose tissue.

There are no surprise histopathologically – only distinctive U-, C-, or J-shaped spicules and mature adipose tissue. Hematopoietic elements may be present.

Whether all reported cases are the same entity since the calcification in some are more solid and “lumpy” than alphabetical.

