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

AANP Companion Meeting

USCAP 2013

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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 oncocytoma 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 oncocytoma, or even between pituicytoma and spindle cell oncocytoma.
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

CRANIOPHARYNGIOMA

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**