Practical Procedures for Problematic Parathyroids and Pituitaries

Sylvia L. Asa, M.D., Ph.D.
Pathologist-in-Chief and Medical Director, Laboratory Medicine Program
University Health Network
Senior Scientist, Ontario Cancer Institute
Professor, Department of Laboratory Medicine and Pathobiology
University of Toronto

Pituitary Problems

The autopsy pituitary:
- Grossing and handling

The surgical specimen:
- Pituitary or not?
- If pituitary, hyperplasia or adenoma?
- If adenoma, what kind?
- What is this inflammation all about?

The Autopsy Pituitary
Pitfalls in Autopsy Pituitaries

- Infarcts and fibrosis
- Basophil invasion of the posterior lobe
- Crooke’s hyaline change
- Hypophysitis
- Tumors
- Tumors
- Tumors

The Surgical Biopsy:
Is This Pituitary?

- Pituitary adenomas (or very rare carcinoma)
- Craniopharyngiomas, cysts
- Other CNS lesions
  - neuronal tumors, paraganglioma, pituicytoma, glioma, meningioma, schwannoma
- Vascular and mesenchymal tumors
  - spindle cell oncocytoma, granular cell tumors, chordomas
- Lymphomas, leukemias, histiocytoses, germ cell tumors
- Metastatic

What Is This Cyst?

- Rathke cleft cyst vs Craniopharyngioma
- Arachnoid Cyst
- Dermoid vs Epidermoid
This is Pituitary; Now What?

- Make sure you don’t miss hyperplasia:
- Do a Retic stain!

Pituitary Hyperplasia: Reticulin

It Is Adenoma – Is That Enough?

- NO!
- But what now?
Prognostic Markers in Pituitary Tumors

- Best is still tumor type
- Clinicopathologic features – size, invasion
- Others suggested:
  - MIB-1 (<5%, 5-15%, >15%)
  - PTTG (same idea as MIB-1)
  - p27 (lost in corticotroph adenomas)
  - p53 (no proven value)

Pituitary Tumor Classification

<table>
<thead>
<tr>
<th>Functioning</th>
<th>Silent</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH excess</td>
<td>Corticotroph adenoma</td>
</tr>
<tr>
<td>GH excess</td>
<td>DG/GG somatotroph</td>
</tr>
<tr>
<td>PRL excess</td>
<td>Lactotroph acidophil stem cell</td>
</tr>
<tr>
<td>TSH excess</td>
<td>Thyrotroph</td>
</tr>
<tr>
<td>Gonadotropin Excess</td>
<td>Gonadotroph</td>
</tr>
<tr>
<td>Plurithemonal</td>
<td>Unclassified</td>
</tr>
</tbody>
</table>

Immunohistochemical Classification of Pituitary Adenomas

<table>
<thead>
<tr>
<th>Major Component</th>
<th>Other Reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH-PRL-TSH</td>
<td>Pit-1</td>
</tr>
<tr>
<td>GH, DG</td>
<td>α-subunit</td>
</tr>
<tr>
<td>GH, PRL</td>
<td>keratin</td>
</tr>
<tr>
<td>TSH</td>
<td>α-subunit, ER</td>
</tr>
<tr>
<td>ACTH</td>
<td>ER</td>
</tr>
<tr>
<td>Gonadotropin</td>
<td>αα-subunit</td>
</tr>
<tr>
<td>Unclassified</td>
<td>Tpit</td>
</tr>
<tr>
<td></td>
<td>SF-1</td>
</tr>
<tr>
<td></td>
<td>??</td>
</tr>
</tbody>
</table>
Pitfalls in Cushing’s Disease

- Usual finding: basophil microadenoma
- Problem 1: Large chromophobe adenoma
- Problem 2: No adenoma
- Problem 3: Crooke’s cell adenoma

Sparsely Granulated Corticotroph Adenoma

Cushing’s Disease: The Case of the Missing Adenoma

- Cushing’s vs Pseudo-Cushing’s
  - Crooke’s hyaline change
Cytology of “Normal” Gland

ACTH and Cam 5.2

Crookes’ Cell Adenoma

Keratin accumulation in cytoplasm
**Acromegaly-Gigantism (↑GH): Differential Diagnosis**

- Adenoma vs hyperplasia
- Somatotroph vs Mammosomatotroph adenoma
- Densely vs Sparsely granulated adenoma
- Gangliocytoma

**Somatotroph Hyperplasia**

**Ectopic GRH in Endocrine Tumors**
Acromegaly-Gigantism (↑GH); Pituitary Adenomas
- Somatotroph vs Mammosomatotroph
- Densely vs Sparsely granulated (keratin)

Sellar Gangliocytoma with Pituitary Adenoma

Prognostic and Therapeutic Considerations in Acromegaly
- Hyperplasia
  » look for source of GHRH excess
- Densely granulated somatotroph adenoma
  » likely responsive to somatostatin analogue therapy
- Sparsely granulated somatotroph adenoma
  » may be due to altered GH autoregulation
  » may be candidates for GH antagonist therapy
- Mammosomatotroph adenoma
  » possible response to dopaminergic agents
Pitfalls in Hyperprolactinemia

- Adenoma vs Other Tumor
- Adenoma vs Hyperplasia
- Adenoma vs Lymphocytic Hypophysitis
- Sparsely Granulated vs Densely Granulated
- Acidophil Stem Cell Adenoma

Inflammatory Lesions of the Pituitary: Hypophysitis

- Lymphocytic hypophysitis
- Granulomatous hypophysitis
- Xanthomatous hypophysitis
- Infundibulo-neurohypophysitis
- Secondary hypophysitis

Lymphocytic Hypophysitis: Histology
Granulomatous Hypophysitis

- The least common form of primary hypophysitis
- Resembles xanthomatous inflammatory processes elsewhere, such as xanthomatous cholecystitis, endometritis or pyelonephritis
- Cystic on radiologic or surgical evaluation
- May be a response to ruptured cyst???

Xanthomatous Hypophysitis

- Rare
- Present with isolated diabetes insipidus
- Localized enlargement of posterior lobe/stalk
- Lymphoplasmacytic infiltrate resembling LH
- Autoimmune disorder

Infundibulo-Neurohypophysitis
Pitfalls in TSH Hypersecretion

- Thyrotroph hyperplasia
  - H&E
    - large chromophobic “thyroidectomy cells”
    - interspersed acidophils and basophils
  - PAS
    - positive globules
  - Reticulin stain
    - acini intact, enlarged

Pituitary TSH Excess

- Hyperplasia
  - H&E
    - monotonous population of elongated chromophobes
    - marked nuclear atypia
    - nil else
  - PAS
    - positive globules
  - Reticulin stain
    - acini disrupted

- Adenoma
  - H&E
    - monotonous population of elongated chromophobes
    - marked nuclear atypia
    - nil else
  - PAS
    - positive globules
  - Reticulin stain
    - acini disrupted

Histology: Thyrotroph Hyperplasia

- H&E
- PAS
- Reticulin
The Role of the Pathologist in the Management of Patients with Pituitary Pathology

- To ensure correct diagnosis
- To guide correct management
- To be responsible for ongoing investigations to determine pathogenesis and future therapies

References

**Parathyroid Problems**

- Parathyroid or not?
- If parathyroid, hyperplasia or adenoma?
- What about carcinoma?

---

**The “Old” Approach to Parathyroid Surgery**

- Identify all parathyroid glands
- Remove dominant pathology
- Biopsy all other glands
  - Put the onus on the Pathologist to make the diagnosis of hyperplasia vs adenoma
  - Often wrong or impossible!

---

**The “New” Approach to Parathyroid Surgery**

- Radioguided surgery identifies the dominant gland
- Limited approach traumatizes only that gland
- Intraoperative PTH measurement confirms resection of culprit lesion
  - Pathologist only needs to confirm that abnormal (cellular) parathyroid tissue was resected
**Parathyroid vs Thyroid on FNA**

- Parathyroid has delicate vascular patterns, small cell size and numerous, disperse, stripped nuclei
- Parathyroid CAN have intranuclear inclusions
- IHC can be applied to FNA samples
- Cyst fluid can be tested for PTH to distinguish a parathyroid cyst from a cystic thyroid lesion

**Parathyroid Identification at Intraoperative Consultation**

- PTH vs Thyroid vs Lymph node or Thymus
- Smaller follicles than thyroid
- Clear cells usually PTH
  - Fat stains can help
    - NB intracytoplasmic fat
- Hassal corpuscles
- Sometimes impossible

**IHC: Thyroid vs Parathyroid Tumor**

- Chromogranin +
- Parathyroid hormone +
- TTF-1 negative
**Hyperplasia vs Adenoma**

- **Hyperplasia**
  - multiple (>1) glands
  - poorly encapsulated
  - diffuse or nodular
  - comparable areas in adjacent glands
  - all 3 cell types
  - mitoses but little pleomorphism
- **Wrong**
- **Doesn’t matter**

- **Neoplasia**
  - solitary
  - encapsulated
  - nodule
  - adjacent normal gland
  - no hypercellularity
  - chief cells predominate
  - nuclear pleomorphism

---

**Primary Hyperparathyroidism: Adenoma**

- Image of a parathyroid gland
- Histological image of parathyroid gland

---

**Primary Hyperparathyroidism: Adenoma**

- Image of a parathyroid gland
- Histological image of parathyroid gland
Criteria of Malignancy in Parathyroid Tumors

- Large lesion (> 1g)
- Infiltrative (but so is hyperplasia!)
- Atypia, mitoses, calcification, necrosis and fibrous bands (none definitive)
- Vascular invasion
- Metastases

Worrisome Histologic Alterations Following FNA of Parathyroid *

- Infiltrative
- Atypia, mitoses, calcification, necrosis and fibrous bands
- Following FNA for cytologic diagnosis of mass, aspiration for PTH measurement, or ethanol ablation of known PTH tumor

* Based on WHAFFT, credit to Dr. V. A. LiVolsi

Atypia and Mitoses in Parathyroid Lesions

Hyperplasia

Carcinoma
**Necrosis and Calcification**

- Worrisome
- More common in carcinoma

Not diagnostic alone

---

**Fibrosis: Hyperplasia vs Carcinoma vs Post-FNA**

---

**Criteria of Malignancy: Infiltration**

- Infiltration through capsule in a proven neoplasm
- Also seen in hyperplasia →
**Local Invasion vs Intrathyroidal Parathyroid**
- Intrathyroidal parathyroids are common
- Can mimic thyroid invasion by carcinoma

**Vascular Invasion: Unequivocal Evidence of Malignancy**

**Parathyroid Carcinoma: Metastases**
- Lymph nodes
- Bone
- Lungs
- Adrenals
Ancillary Tests for Borderline Cases

- Parafibromin loss

Immunostains

- Negative Rb ↓
- High MIB-1 ↑
- p53 positivity

References

- DeLellis RA: Tumors of the Parathyroid Gland. Fascicle 6, Third Series, in The Atlas of Tumor Pathology, Armed Forces Institute of Pathology, Washington DC, 1993
- DeLellis RA, Lloyd RV, Heitz PU, and Eng C: Pathology and Genetics of Tumours of Endocrine Organs. Lyons, France IARC Press, 2004