The Case That Taught me the Most

Lester D. R. Thompson
Southern California Permanente Medical Group
www.lester-thompson.com

Presentation

- 51 year old female patient
- Headaches, obstructive symptoms, sinusitis
- Nasal mass
- Biopsy taken
- 0.6 x 0.4 x 0.3 cm
Diagnosis

Neuroendocrine carcinoma, Grade II

But, wait...

Location, Location, Location

◆ Sphenoid sinus > > >
Cavernous sinus
▼ > 3rd ventricle > Nasopharynx, nasal cavity, clivus > > Petrous temporal bone
### Ectopic Sphenoid Sinus Pituitary Adenoma

#### Clinical
- Benign pituitary gland neoplasm occurring separately from and without involvement of sella turcica (a normal anterior pituitary gland)
  - Direct extension from intrasellar pituitary tumors in about 2% should be excluded
- Incidence: Rare in ectopic locations
- Age: Wide range: 16–84 years
  - Mean: 54 years
- Gender: Female > Male (1.3:1)

#### Pathogenesis
- Anterior pituitary primordium appears at about 4 weeks of embryogenesis
- During 8th developmental week, pituitary divides into sellar and pharyngeal parts
  - Supradiaphragmatic attachment to pituitary stalk
  - Cephalic invagination of Rathke pouch (infrasellar)
- Migration into sphenoid or pharynx along craniopharyngeal canal
  - Ectopic pituitary adenomas are derived from these embryologic remnants along the migration path
- Fully functional tissue in these ectopic locations

#### Presentation
- Obstruction, sinusitis, rhinorrhea, discharge
- Headache and pain
- Visual disturbances (diplopia, acuity loss, blurring)
- Endocrine syndrome (Cushing, Acromegaly, Impotency, amenorrhea, galactorrhea)
- Asymptomatic (10%)

#### Laboratory Tests
- All ectopic hormones can be measured serologically or via stimulation/suppression testing
  - ACTH, GH, TSH, prolactin, cortisol
  - Releasing hormones can also be measured
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Imaging Findings

- Intrasphenoidal mass with expansion and/or erosion
  - Sella may be involved by upward extension, but usually normal
  - Strong enhancement post contrast
- Define extent and location of tumor
- Imaging usually suggests chordoma, nasopharyngeal carcinoma, or metastatic tumor

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Macroscopic Features

- Polypoid and pedunculated mass within sphenoid sinus
  - May expand bone into adjacent structures
- Size: Range: 0.5 to 8.0 cm
  - Mean: 2.9 cm
- Tumor size does not seem to correlate with symptom severity
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Histologic Findings

- Intact surface epithelium
- Submucosal location of unencapsulated tumor
- Invades into subepithelial stroma and bone
  - No perineural or vascular invasion
- Many patterns
  - Solid, organoid, glandular, insular, festoons, ribbons, single file, rosettes—pseudorosettes, papillary, cystic
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Histologic Findings

- Concretions/secrections may be present
- Tumor cellularity usually low to medium
  - Highly cellular (34%)
- Necrosis present (25%)
- Mitoses present, but not atypical
- Fibrovascular, hemorrhagic to sclerotic background stroma
  - Rarely, calcified with psammomatoid bodies
- Invades around minor mucoserous glands
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Histologic Findings

- Somewhat monotonous population of epithelial cells
  - Polygonal, plasmacytoid, cuboidal, spindled
  - Round or oval nuclei
  - "Salt-and-pepper," clumped chromatin
  - Majority have small nucleoli
    - May see prominent nucleoli (20%)
  - Eosinophilic, granular, amphophilic or clear, eccentrically located cytoplasm
- Profound pleomorphism (15%)
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Histologic Findings

- Intranuclear cytoplasmic inclusions usually present in some cells (80%)
- Multinucleated tumor cells (56%)
- Fibrous bodies (10%)
Positive:
- CK-Pan (AE1/AE3) 79%
- CAM5.2 61%
If Both: 86%
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Immunohistochemistry

**Positive:**
- CK-Pan (AE1/AE3) 79%
- CAM5.2 61%
- If Both: 86%

**Negative:**
- CK7
- CK5/6
- p63

Immunohistochemistry

**Positive:**
- Synaptophysin: 97%
- CD56: 91%
- NSE: 76%
- Chromogranin-A: 71%
- CD99: 40%

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Immunohistochemistry

**Positive:**
- Prolactin 59%
**Immunohistochemistry**

**Positive:**
- Prolactin: 59%
- FSH: 47%
- LH: 37%
- ACTH: 33%
- TSH: 29%
- GH: 26%

**Calcitonin**

**Positive:**
- Prolactin: 59%
- FSH: 47%
- LH: 37%
- ACTH: 33%
- TSH: 29%
- GH: 26%
- Calcitonin: 20%

**Electron Microscopy**

- Intracytoplasmic neurosecretory granules
  - Number, size, shape, and type of granules dependent on tumor hormone production
- Often show prominent rough endoplasmic reticulum, large Golgi apparatus

*No pituitary transcriptions factors performed: Pit-1, T-pit, SF-1, ER-α, and GATA-2*
**Treatment**

- Complete surgical removal is treatment of choice
- Medical/hormonal manipulation
  - Dopamine-agonists (bromocriptine), somatostatin analogs (octreotide), corticosteroids (hydrocortisone, prednisone), thyroxine
- Stereotactic radioablation
  - For larger or incompletely removed tumors

**Prognosis**

- Excellent prognosis
  - 96% are Alive or Dead with no evidence of disease (mean follow-up: 10.5 years)
  - 4% died with disease (0.8 years)
  - 14% persistence/recurrence (mean, 2.1 years)
    - Managed with surgery or radiation
- Metastases are not reported

**Differential Diagnosis: Olfactory Neuroblastoma**

- Ethmoid sinus, destructive tumor, lobular architecture, syncytial architecture, neurofilament background, rosette formation, prominent nucleoli and mitoses in high-grade tumors
- **Positive:** Chromogranin, synaptophysin, CD56, S100 protein (sustentacular)
- **Negative:** CK-pan (usually); peptide markers

**Ectopic Sphenoid Sinus Pituitary Adenoma**
**Differential Diagnosis:**

**Ewing/PNET**

- Small round blue cell tumor, sheets, tumor necrosis; finely distributed chromatin, mitoses
- **Positive:** FLI-1, CD99, SNF5, NSE, β-catenin (membrane)
- **Negative:** Chromogranin, synaptophysin, keratin (usually)
- **EWS/FLI1** translocation
Differential Diagnosis: Neuroendocrine Carcinoma

- High-grade malignant neoplasm, syncytial architecture, “salt-and-pepper” nuclear chromatin, molding, mitoses, necrosis
- **Positive:** Keratin, chromogranin, synaptophysin, CD56
- **Negative:** Pituitary hormones, pituitary transcription factors

Differential Diagnosis: Sinonasal Undifferentiated Carcinoma

- Rapidly growing, midline destructive tumor, epithelial proliferation of undifferentiated cells, significant pleomorphism, mitoses, necrosis, perivascular and perineural invasion, lacking squamous/glandular features
- **Positive:** CK-pan, p63, CK5/6
- **Negative:** Neuroendocrine (rarely positive), pituitary hormones, pituitary transcription factors
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Differential Diagnosis: Nasopharyngeal Carcinoma

- Nasopharynx, epithelial proliferation of undifferentiated cells, large cells, high nuclear to cytoplasmic ratio, vesicular chromatin, prominent nucleoli, many mitoses, lymphoid stroma
- **Positive**: CK-pan, CK5/6, p63, EBER
- **Negative**: Neuroendocrine markers, pituitary hormones and transcription factors
Differential Diagnosis:
Meningioma

- Cellular tumors with whorled appearance, frequent calcifications, intranuclear cytoplasmic inclusions, coarse nuclear chromatin
- **Positive**: EMA, CK7
  - Rarely, S100 protein
- **Negative**: Neuroendocrine and pituitary hormones
Differential Diagnosis: Mucosal Melanoma

- Dyscohesive epithelioid to spindled tumor cells, junctional proliferation, pigmented, intranuclear cytoplasmic inclusions, eccentric nuclei, profound pleomorphism, mitoses, necrosis
- **Positive**: S100 protein, HMB-45, Melan-A,
- **Negative**: Keratin, neuroendocrine markers, pituitary hormones and transcription factors
Think very broadly when confronted with Sinonasal Tract “Small Round Blue Cell” tumors (MR. SLEEP)

- H&E features are often characteristic
- Let H&E guide ancillary/pertinent studies
- There will be immunohistochemistry overlap
- Targeted molecular studies as needed

Always think of ectopic pituitary adenoma in a sphenoid sinus tumor no matter what they look like!