Pituitary Adenomas

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Outline

1. Epidemiology
2. Anatomical considerations
3. Pathology
4. Clinical presentation
5. Diagnostic workup
6. Management: Surgery, Systemic Therapy, Radiation
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Epidemiology

- Pituitary adenomas comprise 10-15% of CNS neoplasms
  - Median age at diagnosis is 40 years
  - They are the most common suprasellar mass in adults (craniopharyngiomas are more common in children)
    - Incidental adenomas are seen in around 25% of autopsies

- They are sometimes categorized based on size:
  - Microadenoma = less than 1 cm
  - Macroadenoma = greater than 1 cm
Anatomical Considerations

- The pituitary gland is made up of two lobes, each of which is responsible for the regulation of different hormones
  - Anterior lobe (FLAT PiG)
    - FSH / LH / ACTH / TSH / PRL / GH
  - Posterior lobe
    - Oxytocin / ADH

- The pituitary gland lies near the optic chiasma and cavernous sinus
  - This has clinical presentation AND treatment implications!
Pathology

- Masson’s trichrome staining is used for easy distinction between acidophils and basophils
  - This trichome includes Weigert’s Hematoxylin, Biebrich scarlet-acid fuschin solution, and Aniline blue

- Secretory function can be elucidated by histological appearance!
  - **Acidophils:** Lactotrophs (PRL-secretors) and somatotrophs (GH-secretors) stain well with acidic dyes
  - **Basophils:** Corticotrophs (ACTH-secretors), gonadotrophs (FSH-, LH-secretors), and thyrotrophs (TSH-secretors) stain well with basic dyes
  - **Chromophobes:** Cells which do not take up stain are called chromophobes, (or clear-cells); these are classically non-secretory or hormone-depleted

- Certain histologies (i.e.: **Atypical** and **Crooke cell adenomas**) are noted to be have aggressive courses
Pituitary tissue is routinely stained with PRL, ACTH, GH, TSH, LH, and FSH to more specifically characterize functional status.
Subtypes and clinical presentations

**Functional Tumors** (70% of tumors)
- Prolactin
  - Prolactinoma
  - About 30% of tumors
- ACTH
  - Cushing disease
  - About 15% of tumors
- GH
  - Acromegaly
  - About 25% of tumors
- TSH
  - Hyperthyroidism
  - Less than 1% of tumors

**Non-Functional Tumors** (30% of tumors)
- These often present incidentally or with compressive symptoms (i.e.: headaches)
- They can also present with apoplexy (sudden hemorrhage), or visual field deficits
Review of Functional Tumors

PITUITARY ADENOMAS

LACTOTROPHS
- Secrete prolactin
- Stimulates breast milk production
- Inhibits ovulation & spermatogenesis

SOMATOTROPHS
- Secrete growth hormone (GH)

CORTICOTROPHS
- Secrete adrenocorticotropic hormone (ACTH)

ADRENAL GLANDS (SECRETE CORTISOL)

THYROTROPHS
- Secrete thyroid stimulating hormone (TSH)

GONADOTROPHS
- Secrete luteinizing hormone (LH)
- Follicle-stimulating hormone (FSH)
Diagnostic Workup

- **History and Physical**
  - Pay special attention to the neurologic examination with visual field testing

- **Labs**
  - Serum prolactin, IGF-1, ACTH and 24-hr urine free cortisol, T3/T4/TSH
  - CSF may be xanthochromic in cases of pituitary apoplexy

- **Imaging**
  - MRI brain
    - Note: an adenoma will have less contrast enhancement than the normal pituitary!
  - Skeletal survey (if acromegaly)

- **Procedures**
  - Given the clinical scenario, a surgery may be required for resection and/or optic chiasm compression
Review of Coronal MRI Anatomy
Pituitary Adenoma: T1c MRI

Note: the adenoma has less contrast enhancement than the normal pituitary!
Therapeutic Management

- **Symptomatic or Mass effect**
  - Yes: **Prolactinoma***
    - *If no visual field defect or apoplexy*
    - Yes: **Dopamine Agonist** (Cabergoline, Bromocriptine)
      - Response: **Observe**
      - No response: **Surgery**
      - GTR: **Observe**
      - STR/Unresectable/Pituitary Carcinoma: **RT (SRS or fractionated)**
  - No: **Observe**

- **All other adenomas**
  - **Observe**

- **Observe**

- **RT and/or medication**

*If no visual field defect or apoplexy*
Principles of Management: Surgery

- Surgery is first-line treatment for symptomatic adenomas apart from prolactinomas.

- There are two approaches:
  - **Transsphenoidal pituitary surgery**
    - This approach is used in majority of cases
  - **Transcranial approach**
    - This approach is used for larger tumors

- Following transsphenoidal surgery:
  - Oncologic outcome varies significantly by tumor size and type
    - Recurrence at 10 years as high as 42% in ACTH adenomas, as low as 1.3% in GH adenomas
  - Hormone normalization occurs in around 70-80% patients in the short-term, falling off to 40% in the long-term
Principles of Management: Systemic Therapy

- Generally, systemic therapy is effective at hormone normalization and occurs quicker than with RT
- Different systemic therapy options are available, with varying efficacies and side effect profiles

- Systemic therapy is first line for **prolactinoma**
  - Dopamine agonists
- Systemic therapy is used at the time of recurrence and/or metastasis for **pituitary carcinoma**
  - Temozolomide

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Medical Therapy if Elevated</th>
<th>Medical Therapy if Deficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin</td>
<td>Cabergoline / Bromocriptine</td>
<td>-</td>
</tr>
<tr>
<td>GH</td>
<td>Octreotide</td>
<td>Growth Hormone</td>
</tr>
<tr>
<td>ACTH</td>
<td>Ketoconazole</td>
<td>Hydrocortisone</td>
</tr>
<tr>
<td>TSH</td>
<td>Carbimazole / Methimazole</td>
<td>Levothyroxine</td>
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Principles of Management: Systemic Therapy

- Dopamine agonists (i.e.: cabergoline and bromocriptine) have side effects that sometimes lead to discontinuation of medical therapy

A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. (Webster et al 1994)
Principles of Management: Radiation

- Radiation therapy is used adjuvantly in:
  - Pituitary carcinoma
  - Subtotal tumor resection

- Radiation therapy is also used for:
  - Unresectable tumors
  - Recurrent tumors
  - Tumors refractory to medical management
    - Theoretical benefit to discontinuing systemic therapy 1-2 months prior to RT, with resumption after RT completion. However, current evidence is equivocal

- Choice of radiation regimen:
  - Stereotactic radiosurgery favored for
    - Smaller tumors (< 3 cm)
  - Favor fractionated radiation for
    - Larger tumors (> 3 cm)
    - Tumors < 3-5mm from the optic chiasm

- Radiation has excellent efficiency, with local control above 90%
  - Hormone normalization may take months – years
The decision between SRS and fractionated regimens will often be decided based on the proximity and subsequent dose to the optic chiasm.

### Stereotactic Radiosurgery

- **Non-secretory:** 14 - 18 Gy
- **Secretary:** 18 - 35 Gy

### Fractionated Radiation

- **Non-secretory:** 45 Gy / 25 fx
- **Secretary:**
  - 50.4 Gy / 28 fx
  - 54 Gy / 30 fx
  - 60 Gy / 30 fx
- **Carcinoma:**
  - 54 Gy / 30 fx
  - 60 Gy / 30 fx

### Optic Chiasm Dose Constraint

- **Single Fraction:** 8-10 Gy Max
- **Five Fractions:** 25 Gy Max
- **Conventional Fractionation:** 54 Gy Max
Radiation Toxicities and Follow-Up

- **Acute:**
  - Fatigue
  - Headache
  - Alopecia

- **Late:**
  - Possible visual deficits, given proximity to optic chiasm
    - Risk is low if dose constraints are respected
  - High risk for hypopituitarism (especially hypothyroidism)
    - Almost all patients will have hormone deficiencies

- **Follow-up:**
  - For secretory adenomas, time-to-hormone normalization following radiation depends on the pre-irradiation hormone level as well as the type of hormone; however, this may occur on the order of years (Jenkins et al 2006)
  - Given risk of hypopituitarism, regular endocrinology follow-up with labs is important
  - MRI brain every 6 months; this can be stretched to yearly scans if imaging is stable

Percentage of all patients achieving a serum GH level less than 2.5 ng/ml (bars) and the mean GH level (line) in the years after pituitary irradiation for acromegaly (Jenkins et al 2006)
History and Physical, Labs

- **History**
  - 19-year-old male with multiple endocrine neoplasia 1 (MEN 1) who presented with nausea, vomiting, dizziness, and headache

- **Physical exam**
  - Bitemporal hemianopia visual defect on exam

- **Labs**
  - Prolactin elevation of 2500 mcg/L (normal <200)

MEN 1 predisposes patients to:
- Pituitary adenoma
- Pancreatic neuroendocrine tumors
- Parathyroid adenoma

Serum prolactin level >200 mcg/L in a patient with a macroadenoma >10mm is diagnostic of a prolactinoma
Radiologic Appearance

T1 coronal with contrast

T1 sagittal with contrast

T1 axial without contrast
Initial Treatment

- **Medications**
  - He was started on cabergoline
  - His prolactin level initially decreased to 1700 mcg/L (normal <200)
  - He continued to have headaches and worsening vision (as well as increased prolactin levels despite cabergoline therapy), so he proceeded to surgery

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Initial Treatment

- **Surgery**
  - A subtotal resection was performed (endoscopic transsphenoidal approach)
  - Pathology returned for a lactotroph adenoma with Ki-67 of 4.7% and increased mitotic activity (associated with a more aggressive clinical course)
  - Subsequent brain MRI showed interval growth of the residual mass, so he was referred for radiotherapy
Radiation: Simulation and Treatment

- Simulation
  - CT without contrast
  - MRI with and without contrast
  - Supine with facemask

- Volumes
  - GTV: tumor seen on T1c MRI
  - CTV: 0.5 - 1 cm
  - PTV: 0.3 – 0.5 cm

- Dose
  - 50.4 Gy / 28 fx

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Clinical Pearls

- Pituitary adenomas are the most common suprasellar mass in adults
- They are classified as functional and non-functional based on their secretory status
- For symptomatic tumors (apart from prolactinomas), surgery is typically first-line therapy (with radiation reserved for treatment refractory cases)
- Radiotherapy can be delivered via SRS or fractionated approaches
  - SRS Doses: 14 – 18 Gy / 1 fx for nonfunctional, 18 - 35 Gy / 1 fx for functional
  - Fractionated Doses: 45 Gy / 25 fx – 54 Gy / 30 fx
- When providing radiotherapy:
  - Special attention must be given to the optic apparatus, as this lies just superior to the treatment field
  - Regular endocrinology follow-up is key, as there is a high risk of hypopituitarism
References

- Online resources
  - Osmosis.org
  - PathologyOutlines.com
  - Radiopaedia.org

- Textbooks
  - Essentials of Radiation Oncology

- Articles

Please provide feedback regarding this case or other ARROcases to arrocase@gmail.com