Challenging Pituitary Cases

Eliza B. Geer, M.D.
eliza.geer@mssm.edu

AACE 25th Congress
May 28, 2016

disclosures

• Investigator for Novartis, Strongbridge, and Chiasma trials

• Consulting/Advisory Boards for
  – Novartis
  – Ipsen
  – Strongbridge
  – Chiasma

• There are no conflicts
Objectives of presentation

• Present 2-3 challenging pituitary cases

• Discuss current treatment options for aggressive/resistant functional pituitary tumors

• Summary

Case #1: BJ

• 58 yo woman who presented in June, 2015 to the ED with progressively worsening right sided vision, retro-orbital headache and decreased facial sensation

• Right pupil 7mm and sluggishly reactive, right ptosis, limited upward and lateral gaze

• CT and MRI Pituitary obtained
Initial MRI
Next step?

- Transsphenoidal surgery
- Craniotomy
- Medical therapy with somatostatin analogue
- Medical therapy with dopamine agonist
- Laboratory testing

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- Craniotomy
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- Laboratory testing
Endocrine Profile

<table>
<thead>
<tr>
<th>Lab</th>
<th>Result</th>
<th>Normal Range</th>
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<tbody>
<tr>
<td>TSH</td>
<td>0.20</td>
<td>0.34-5.6u IU/MI</td>
</tr>
<tr>
<td>FT4</td>
<td>0.64</td>
<td>0.60-1.1 ng/dl</td>
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<tr>
<td>GH</td>
<td>2.71</td>
<td>0.06-5.00 ng/ml</td>
</tr>
<tr>
<td>Prolactin</td>
<td>&gt;201</td>
<td>2.7-19.6 ng/ml; postmenopausal</td>
</tr>
<tr>
<td>LH</td>
<td>0.76</td>
<td>10.9-58.6; postmenopausal</td>
</tr>
<tr>
<td>FSH</td>
<td>1.6</td>
<td>16-113; postmenopausal</td>
</tr>
<tr>
<td>ACTH</td>
<td>13</td>
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</tr>
<tr>
<td>Cortisol</td>
<td>1.3</td>
<td>Micro/dl</td>
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Next step?

- Dilute the prolactin
- Repeat surgery
- Cabergoline 0.25 mg weekly or BIW
- Higher dose cabergoline
- Radiation therapy
- More laboratory testing
- Pituitary endocrine replacement
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### Lab Results

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<tr>
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<tbody>
<tr>
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<td>IGF1</td>
<td>507</td>
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<td>18.2</td>
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<tr>
<td>TSH</td>
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**Next steps?**
- Repeat surgery
- Cabergoline
- Radiation

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*CAB 0.5mg BIW → 0.5 mg qhs
Increase to 1.0mg qhs*
Follow up MRI: October 2015

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*Initial scan*  

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**CAB 0.5mg BIW \(\rightarrow\) 0.5 mg qhs**

*Increase to 1.0mg qhs*

**f/u scan after 4 months of DA**
Follow up MRI: Jan 2016

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Follow up MRI: April 2016

Is this Dopamine Agonist resistance?

- Failure to normalize PRL on maximal tolerated dose of DA
- Lack of radiographic shrinkage/Tumor size reduction ≤ 50%
- Cabergoline resistance: failure to normalize PRL after weekly dose of 1.5 – 3 mg over 3 month period

Molitch *Pituitary* 2003; Molitch *J Neurooncol* 2014; Molitch *Pituitary* 2005; Vroonen *Eur J Endocrinol* 2012
Who is at risk for dopamine agonist resistance?

- Patients with macro/giant prolactinomas
- Patients with invasive tumors
- Men > women; particularly older men


... or (cabergoline-induced) apoplexy?

- Cabergoline and bromocriptine associated apoplexy has been described
  - Lactotroph cell necrosis/fibrosis -> shrinkage & hemorrhage?
- Risk factors for apoplexy (for any pituitary tumor):
  - Large tumor size -> compromised blood supply?
  - Pregnancy
  - ?cystic tumors – a possible sign of outgrowing blood supply
  - Head trauma
  - Anti-coagulation therapy

Next step?

- Continue current management
- Increase cabergoline dose
- Surgery
- Radiation therapy

Indications for surgery for prolactinomas

- Dopamine agonist resistance or intolerance
- Macroadenoma prior to pregnancy
- Use of anti-psychotic medications
- Apoplexy
- CSF leak
- Tumors that are cystic tumors or have intratumoral hemorrhage
- Patient preference
Outcomes for surgery for prolactinomas

- 73.7% microadenomas, 32.4% macroadenomas had normal PRL 1-3 months after surgery
- For DA agonist resistance, surgical success is defined as stabilized/improved vision with normal PRL (+/- DA) – (Smith et al)
  - 65% successful outcome
  - 35% suboptimal outcome (abnormal PRL +/- DA)
- Another study: 7.8% normal PRL post-op (Vroonen et al)
- Post-op PRL generally lower vs. pre-op, and controlled on lower doses of DA
- 7-50% tumors recur post-op


Post-op MRI, May 2016

Pathology: PRL-positive tumor, MIB-1 up to 40%, hemorrhage
PRL 5/16/16: 2,035 ng/ml
Next steps for our patient?

- Conservative monitoring only
- Resume cabergoline
- Radiation therapy
- Chemotherapy
  - Temozolomide
  - Tyrosine kinase inhibitor


Learning points from case 1

- Aggressive/invasive prolactinomas may require higher than typical DA doses
  - But risk for AEs increases; patients may be noncompliant
- Aggressive/invasive prolactinomas may need multimodal therapy, including surgery
- Monitor for apoplexy (or CSF leak) particularly in large prolactinomas
- Consider RT
- Consider temozolomide therapy if failed other treatments and in cases of pituitary carcinoma
Case #2: PD

- 1993: 22 yo woman presented with 80 lb weight gain, striae, hirsutism, acne, facial rounding & plethora, bruising

- 24 hr UFC = 196 mcg, post 1 mg DST cortisol = 19.8 mcg/dL

- Pituitary MRI: 1.5 cm macroadenoma

- 1994: TSS, per report total hypophysectomy, path was positive, post-op hypocortisolism and GC replacement for 1 year

- Hypopituitarism: started thyroid and estrogen replacement
Case PD: CD recurrence

- 2000: presented with clinical recurrence; 24 hr UFC was 698 mcg
- MRI showed 0.5 cm tumor in sella
- 8/00 TSS; pathology +ACTH with MIB-1 = 5%
- Post-operative serum cortisol was 25 mcg/dL, ACTH 90 pg/ml
- 2 weeks post-op (off GCs): 24 hr UFC = 102 mcg, ACTH 102 pg/ml, cortisol 18.4 mcg/dL
- Post-op pituitary MRI did not identify clear residual tumor

What next?

Serial follow up pituitary scans were negative

May 23, 2008
• 3/01: gamma knife radiosurgery (18 Gy)
• 12/01: ketoconazole started
  – UFC = 515 mcg on 400 mg BID
• progressive weight gain, plethora, striae
• 2/03: MRI noted 1.4 x 2 cm lesion in right posterior fossa
• 3/03: suboccipital craniectomy of extra axial tumor, not attached to dura, almost in the arachnoids

PD pathology in 2003 confirmed ACTH-secreting metastasis, thus a pituitary carcinoma
Case: PD continued

- Post-op serum cortisol was 23 mcg/dL, ACTH 220 pg/ml

- MRI of brain/spine: no evidence of additional craniospinal disease

- 5/03 tumor board recommended B/L adrenalectomy

- CS features resolved: lost 90 lbs, hirsutism, plethora & DC fat regressed; ACTH 879 pg/ml

- Additional radiation to treat possible microscopic residual in tumor bed: 5040 Gy to posterior fossa

- Plasma ACTH values ranged from 1,000 – 5,000 pg/ml over next number of years. MRI, PET, and octreotide scans negative

![Source of ACTH undetermined](chart)

Negative brain/spine MRI, PET and octreotide scans

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Second Metastasis in 2015

- She presented in 8/15 with one month of mid–upper back pain
- 1/15: ACTH 3610 pg/ml
- MRI showed 3 enhancing lesions at L1-L2, L3-L4, and L4-L5 level
- Chest, abd, pelvis CT were negative
- 8/24/15: lumbar laminectomy and excision of 3 ACTH tumors

PD pathology in 2015: second metastasis
Case: PD continued

- Post-op:

  8/25/15 ACTH = 4573 pg/ml
  8/28/15 ACTH = 1940 pg/ml

What next?

WHO 2004 Classification

- Typical Pituitary Adenomas
  - Monotonous cells lacking findings seen in atypical adenomas

- Atypical Pituitary Adenomas (~15%) — based on histology
  - Higher mitotic activity
  - Ki-67 (MIB1) >3%
  - Extensive p53 immunoreactivity

- Invasive tumor — based on imaging (e.g. Knosp criteria)

- Pituitary Carcinoma (~0.1-0.2%)
  - Presence of craniospinal or systemic metastatic disease
  - Histologic features of atypical adenomas not required
Medical therapies for aggressive and malignant pituitary tumors

Drug targets for Cushing’s disease
Tumor directed medical therapies for aggressive pituitary tumors

- **Cabergoline**

- **Pasireotide**

- **Temozolomide**

Mixed results using cabergoline for ‘typical’ CD

- No systematic trials have been conducted
- 2 small (N=20) studies show response in 30-40%
- But 20-30% of initial responders later escape, and recent study showed limited response
- Doses are high: up to 7 mg/week
- AEs: nausea, dizziness
- No valvulopathy reported except in one patient

*Pivonello JCEM 2009; Lila, Endocrine Practice 2010; Burman Eur J Endo 2016*
What about cabergoline for aggressive ACTH tumors?

26 year-old woman with Nelson’s: ACTH 2,850 pg/ml, MRI 1.4 x 1.3 cm tumor. Cabergoline 0.5 mg BIW started. . . .
Tumor directed medical therapies for aggressive pituitary tumors

- Cabergoline

- Pasireotide

- Temozolomide
Pasireotide: a multiligand somatostatin analogue

A 12-Month Phase 3 Study of Pasireotide in Cushing’s Disease

Annmaria Colao, M.D., Ph.D., Stephan Petersenn, M.D.,
John Newell-Price, M.D., Ph.D., James W. Findling, M.D., Feng Gu, M.D.,
Mario Maldonado, M.D., Ulrike Schoenherr, Dipl.-Biol., David Mills, M.Sc.,
Luiz Roberto Salgado, M.D., and Beverly M.K. Biller, M.D.,
for the Pasireotide B2305 Study Group®

N ENGL J MED 366:10  NEJM.ORG  MARCH 8, 2012
Pasireotide therapy for Cushing’s disease

At month 12:
13% of 600 μg group
25% of 900 μg group
Achieved normal UFC

55 yo woman with CD since age 15, s/p BLA; developed Nelson’s and underwent multiple TSAs and RT. When she developed third nerve palsy and suprasellar tumor enlargement she was started pasireotide LAR 60 mg/28 days. . .

*J Clin Endocrinol Metab* 2013
Tumor directed medical therapies for aggressive pituitary tumors

- Cabergoline
- Pasireotide
- Temozolomide
Temozolomide

- Oral alkylating agent approved for GBM
- Crosses BBB, 100% oral bioavailability
- Not cell cycle specific -> useful for slow-growing tumors

Several small case series show temozolomide to be effective in treating aggressive pituitary tumors

- First reports in 2006:
  - Lim et al. Lance Oncol 2006: 1 prolactin carcinoma
  - Syro et al. Clin Endocrinol 2006: 1 prolactin tumor
  - Fadul et al. J Neurosurg 2006: 2 pituitary carcinomas

  . . . additional case reports published

- French series (Raverot): 8 patients (5 carcinomas – 2 ACTH, 1 PRL); 3 aggressive tumors (1 PRL, 2 ACTH) given TMZ for 4-14 cycles
  - 3/8 responded (tumor shrinkage, hormonal reduction)
  - 3 cycles sufficient to identify responders

Raverot J Clin Endocrinol Metab 2010
• 24 patients with aggressive pituitary tumors (16 locally aggressive, 8 carcinomas)
  – 9 PRL, 4 ACTH, 4 GH, 2 GH/PRL
• Treated with TMZ for median of 6 months, median f/u 32 months
• Complete tumor regression in 2 carcinomas
• Partial regression (35-80%) in 5 locally aggressive, 2 carcinomas
• Median MGMT staining was 9% in responders vs. 93% in nonresponders

Back to the case . . .

• First: measured ACTH after am hydrocortisone dose
  – 8/25/15 ACTH = 4573 pg/ml; 8/28/15 ACTH = 1940 pg/ml
  – 10/14/15: ACTH 328 pg/ml (after taking HC)

• Octreotide scan was negative, as was extensive imaging

• But she has elevated ACTH values, and known metastatic disease

• In 10/14 we started cabergoline, titrated up to 1 mg qhs
  – 11/5: ACTH 813 pg/ml; 11/17/15: ACTH > 1250 pg/ml -> D/C’d cabergoline

• 12/11/15 started pasireotide 0.6 mg BID -> 12/24/15 ACTH 78 pg/ml

• 2/4/16: ACTH 389 pg/ml (all samples 8 am after taking HC)
Case continued. . .

- Feb, 2016 pituitary and spine MRI: no interval change; **ACTH 389 pg/ml - 8 am after taking HC (nl to 50)**

- 3/10/16 stopped pasireotide due n/v/diarrhea

- 3/11/16 **ACTH 938 pg/ml**; 4/14/16: **ACTH 1198 pg/ml**

- **Plan:**
  - monitoring with q 3 month MRI imaging
  - For Gallium 68 PET/CT
  - Consider temozolomide + xeloda if new metastasis is identified

Learning points from case 2

- Not all pituitary tumors are benign

- The only two tumor directed endocrine therapies:
  - **Cabergoline**: Few cases of Nelson’s only (no carcinoma)
  - **Pasireotide**: one case of Nelson’s; 1 ACTH carcinoma (+TMZ)

- **Temozolomide** is an effective option for aggressive pituitary tumors that have failed other therapies
  - 60% of published cases and 60% of ACTH tumors respond
  - Recurrence after initial response occurs in some patients
  - Screen for thrombocytopenia; cerebral hemorrhage reported
  - Combination with xeloda or pasireotide could be effective

**New pituitary directed targets/therapies are needed!**
Case 3

Case #3: GC

- 69 yo man presented to us in 2/16

- Gynecomastia at age 50. Biopsy, mammogram, and US normal

- PRL 40. 2008 CT head: empty sella. Started CAB 0.5 mg q wk

- In 2013 his GH & IGF-1 were noted to be high: IGF1 470 (nl to 279), GH 4.9 (baseline) -> 5.2 -> 5.0 (one hour), PRL 11.2

- 2013: Started somatuline 60 mg, increased to 120 mg per month
Review of additional prior records

- 2008: CT chest/abd/pelvis negative; in 6/12 negative
- 2013-2014: IGF-1 values elevated 299-524 (nl to 279)
- 2014: Octreotide scan negative
- 2015 MRI pituitary: partially empty sella, no adenoma
- Recent IGF-1 on maximum dose somatuline was elevated
- Comorbidities: OSA, HTN, impaired fasting glucose

What is the likely source of his acromegaly?

- Significance of elevated PRL:
  - Co-secreting (PRL and GH) tumor?
  - Suggests pituitary source

- Pituitary tumor that underwent apoplexy, which could explain the finding of empty sella?
  - But expect apoplexy would ‘treat’ the acromegaly - IGF1 would be normal

- Ectopic source of acromegaly (1% of cases)
  - GHRH excess:
    - Central causes: hypothalamic hamartomas, choristomas, ganglioneuromas
    - Peripheral causes: bronchial carcinoids, pancreatic islet cell tumors, SCLC, adrenal adenomas, medullary thyroid carcinomas, pheochromocytomas
  - Ectopic GH excess: pancreatic islet cell tumors, lymphomas, (iatrogenic)
Ectopic acromegaly

- Only 99 patients reported
- Possible association with MEN-1
- Pituitary hyperplasia from ectopic GHRH can be misdiagnosed as a pituitary tumor and lead to unnecessary pituitary surgery

Ghazi, Endocrine, 2013; Melmed NEJM 1985; Beuschlein NEJM2000; Thorner JCI 1982
Next steps?

- Repeat/additional imaging
  - CT?
  - Octreotide scan?
  - MIBG?
  - Gallium 68 PET/CT?

- Check additional neuroendocrine markers

- Add pegvisomant to somatuline

- Switch to pasireotide

Next steps?

- Imaging:
  - Repeat CT
  - Repeat octreotide scan
  - MIBG: sensitivity 83-100%, Specificity 95-100%
  - Gallium 68 PET/CT imaging: Sensitivity 93%, specificity 91% for thoracic and GI NETs

- Check additional neuroendocrine markers

- Add pegvisomant to somatuline

- Switch to pasireotide

Treglia Endocrine 2012; Oberg Endocrine 2012
Further evaluation ongoing

- **Neuroendocrine assessment normal** (including Insulin, glucose, neuron specific enolase, glucagon, serotonin, alpha-subunit, pancreatic polypeptide, chromogranin A, calcitonin)

- Switched to **pasireotide**: IGF-1 normal; glucose elevated

- Repeat **CT imaging**: 4 mm left lower lobe pulmonary nodule.

- Plan for repeat **octreotide scan** (will need to be off pasireotide for 4 weeks) then Gallium 68 PET/CT imaging if needed

- Attempting to measure GHRH (test not approved by NYS DOH)
  - Inter Science Institute

Learning points from case 3

- In patients with hyperprolactinemia, check GH/IGF1 axis
  - Co-secretion is common

- Pasireotide is not for everyone, due to hyperglycemic effect
  - But can be useful in patients who are not controlled on conventional somatostatin analogues

- Ectopic acromegaly is rare – usually acromegaly is not hard to localize (unlike Cushing’s)
THANK YOU

eliza.geer@mssm.edu