NEW DIAGNOSIS OF PITUITARY ADENOMA IN PREGNANCY

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Endorama
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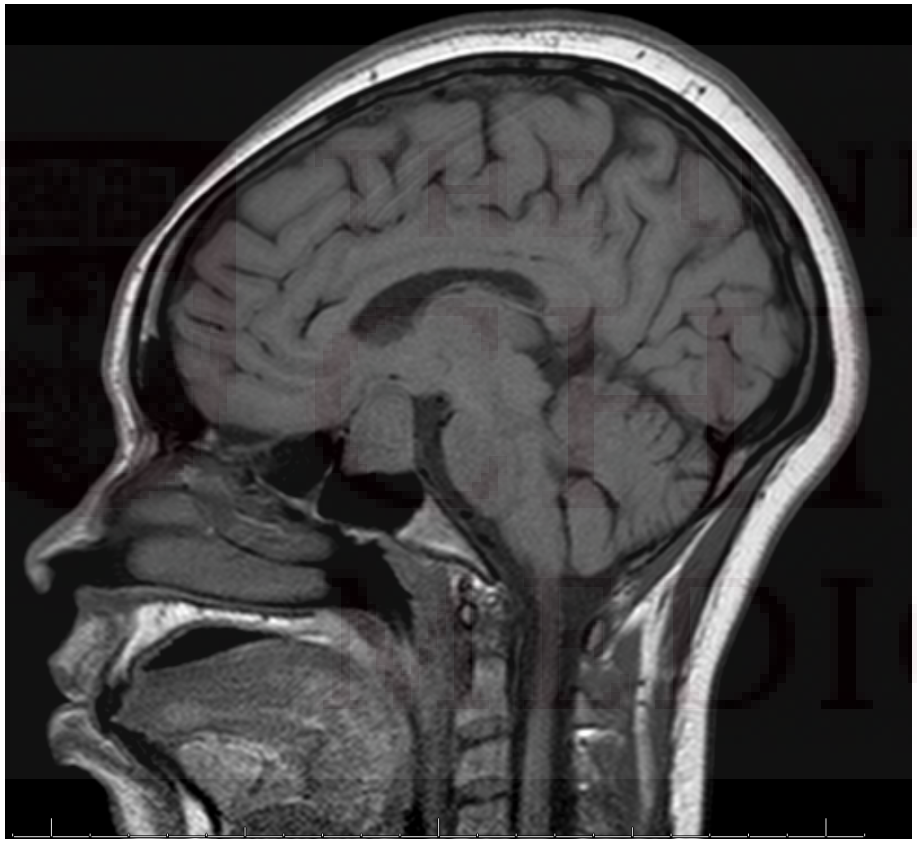
29 yo F in her third trimester of pregnancy

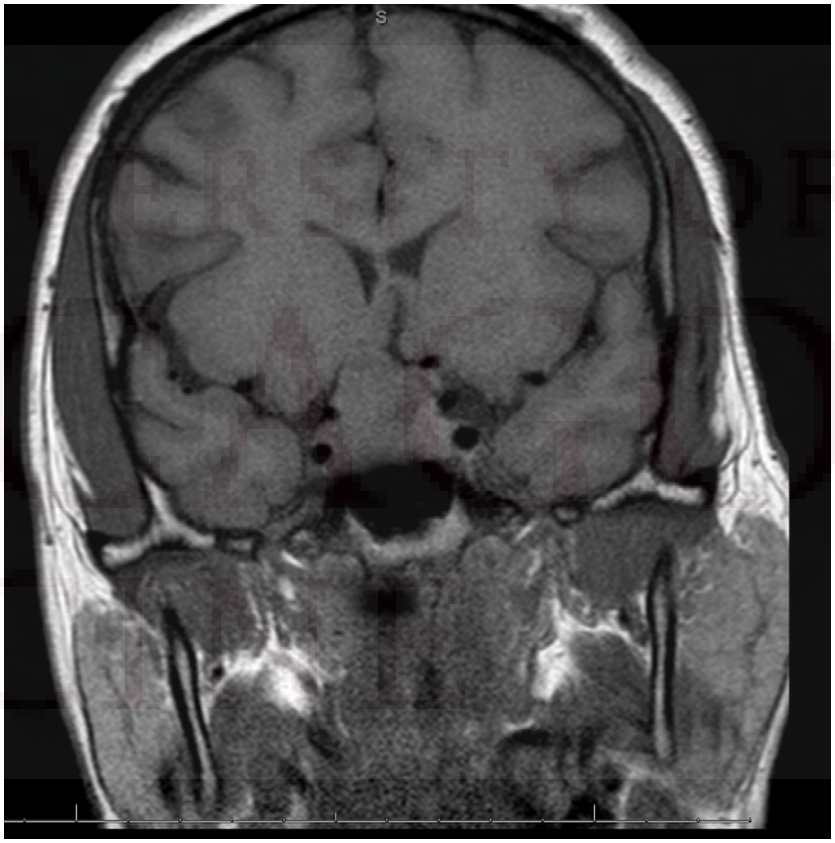
- Initially presented 2 months prior to OBGYN for HA which was resolved with fluids and fioricet
- Presented to ED 2 weeks prior for blurred vision, was treated for a migraine and discharged with expedited ophthalmology follow up.
- Ophtho exam was concerning for a defect at the level of the retina or the optic tract so MRI brain was obtained that showed a large sellar mass.

Consult pager:

Please call neurosurgery regarding pregnant patient with large sellar mass.

Imaging





Right sellar tumor with suprasellar extension measuring up to 23 mm [which] exerts a mass effect upon the optic apparatus and likely represents a pituitary macroadenoma with prior intratumoral hemorrhage

Labs obtained in ophtho clinic show:

- TSH 0.90 (0.3-4.00 mcU/mL)
- fT4 1.12 (0.9 – 1.7 ng/dL)

- LH 0.3 iU/ML
- FSH <0.1 iU/mL

- **Prolactin 208.40** (4.8-23.3 ng/mL)

- **ACTH 60.6** (<52 pg/mL)

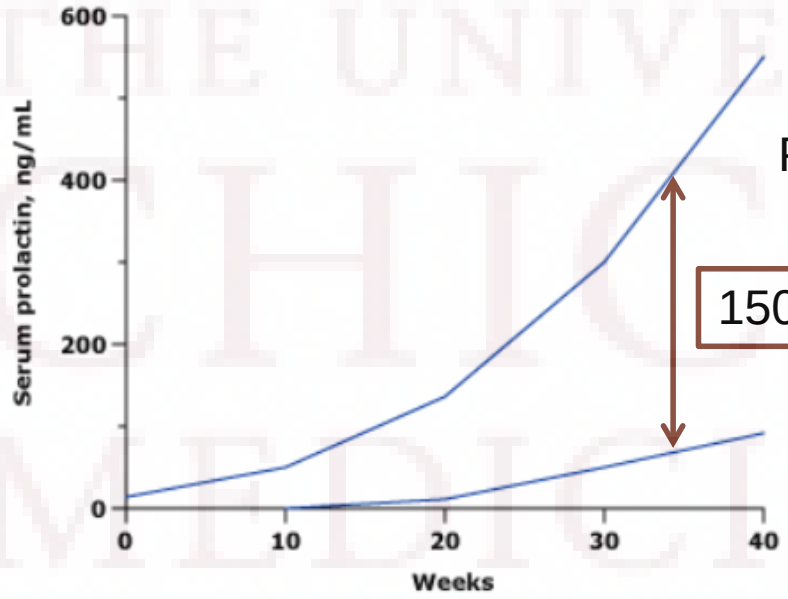
- IGF1 **Pending**

All labs drawn at 12PM

What other information or additional work up would you like?

Normal Prolactin levels in pregnancy

Serum prolactin concentrations increase during pregnancy



Patient's prolactin: 208 ng/mL

150-400 ng/mL

Serum prolactin concentrations as a function of time of gestation, showing the increase in prolactin as pregnancy progresses. The zone lines represent the range of values that can be seen.

Data from Tyson JE, Ito P, Guyda H, et al. Studies of prolactin secretion in human pregnancy. Am J Obstet Gynecol 1972; 113:14.

Additional history

- Reduced vision on R inferiorly and laterally
- Vision changes x3 weeks with slow progressive decline, believes it has been stable over the past 1 week, however family member states that her vision is worse from 1 week ago
- No difficulty conceiving previously, no irregular periods or galactorrhea. No personal hx of thyroid or pituitary problems
- FH negative for endocrinopathies, tumors

ROS

Constitutional: Positive for **fatigue**. Negative for activity change, appetite change and fever.

HENT: Positive for nosebleeds. Negative for congestion, sinus pressure and trouble swallowing.

Eyes: **Reduced vision inferiorly**

Respiratory: Negative. Negative for cough, shortness of breath and wheezing.

Cardiovascular: Negative. Negative for chest pain and palpitations.

Gastrointestinal: Positive for **Nausea which is new today**. Negative for abdominal pain, constipation and diarrhea.

Endocrine: **Sellar mass as above**

Genitourinary: Negative. Negative for dysuria, flank pain and frequency.

Skin: Negative.

Neurological: Positive for **headaches**. **Negative for dizziness, syncope, weakness and light-headedness.**

Psychiatric/Behavioral: Negative.

Past Medical History

PMH
- None

PSH
- D&C

Social Hx
- No Tobacco
- No EtOH
- No other drugs or supplements
- LAHW son (5 yo)

Medications
- ASA (PRN HA)
- PNV

Allergies: NKDA

Family Hx
- No Endocrinopathies
- No Malignancies

Physical Exam in clinic

Vitals: BP 114/70, HR 114, Wt 76.2 kg, Ht 167.6 cm

Constitutional: She is oriented to person, place, and time. She appears well-developed and well-nourished. No distress.

HEENT: Normocephalic and atraumatic. Oropharynx is clear and moist. **EOM are normal. Pupils are equal, round, and reactive to light. Visual fields impaired on R inferiorly on confrontation**

Neck: Neck supple. No thyromegaly present.

Cardiovascular: Regular rhythm. No murmurs. **Mild tachycardia**

Pulmonary/Chest: Effort normal and breath sounds normal. No respiratory distress. She has no wheezes. She has no rales.

Abdominal: Soft. There is no tenderness. There is no guarding. **Gravid uterus**
Musculoskeletal: Normal range of motion. She exhibits no edema or deformity.
Neurological: She is alert and oriented to person, place, and time. **No other CN deficits.**

Skin: Skin is warm and dry.
Psychiatric: She has a normal mood and affect. Her behavior and judgement are normal.

What would you like to do?

- TSH 0.90 (0.3-4.00 mcU/mL)
- fT4 1.12 (0.9 – 1.7 ng/dL)

- LH 0.3 iU/ML
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- **Prolactin 208.40** (4.8-23.3 ng/mL)

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Hx:

- 35 weeks pregnant
- Epistaxis
- Nausea
- Visual fields impaired – stable vs mildly progressive
- HA intermittently – now none

Exam:

- Tachycardia, impaired vision, gravid uterus; generally appears well.

A) Monitor as outpatient until deliver with close follow up
B) Admit for additional monitoring and further evaluation

Recommendations

- Admit to L&D for expedited evaluation given continued and possibly progressive visual field deficits
- Expedited Neurosurgery and Ophthalmology evaluation inpatient
- Obtain 8AM Cortisol and ACTH, prolactin dilution to evaluate for Hook Effect and Total T4 as the free T4 assay is unreliable during pregnancy

  - Total T4 11.3 ug/dL
  - ACTH 27.7 pg/mL, Cortisol 12.6 ug/dL (9AM)*
  - Repeat prolactin with dilution: 189.6 ng/mL

* High-dose dexamethasone x48h given per OB and NSGY to promote fetal lung maturation and reduce ?intracranial inflammation

Would you consider use of a Dopamine agonist in this setting?

Use of dopamine agonists prior to and during early pregnancy

- Both are Pregnancy Category B
- With <6 weeks of use, no increase in spontaneous abortions, ectopic pregnancies, trophoblastic disease, multiple pregnancies, or congenital malformations compared to the general population with either drug
- Cabergoline is easier to dose and better tolerated
- There is more data for bromocriptine, however either is a reasonable choice
- If trying to get pregnant, consider using contraception for the first 2-3 cycles to more quickly identify and missed period and thus a pregnancy

Molitch. European Journal of Endocrinology (2015) 172, R205–R213

Pregnancy outcomes with short-term (<6 weeks) use of a dopamine agonist

	Bromocriptine (*n* (%))	Cabergoline (*n* (%))	Normal (%)
Pregnancies	6239 (100)	968 (100)	100
Spontaneous abortions	620 (9.9)	73 (7.5)	10–15
Terminations	75 (1.2)	63[d] (6.5)	20
Ectopic	31 (0.5)	3 (0.3)	1.0–1.5
Hydatidiform moles	11 (0.2)	1 (0.1)	0.1–0.15
Deliveries (known duration)	4139 (100)	705 (100)	100
At term (>37 weeks)	3620 (87.5)	634[e] (89.9)	87.3
Preterm (<37 weeks)	519 (12.5)	71 (10.1)	12.7
Deliveries (known outcome)	5120 (100)	629 (100)	100
Single births	5031 (98.3)	614 (97.6)	96.8
Multiple births	89 (1.7)	15 (2.4)	3.2
Babies (known details)	5213 (100)	822 (100)	100
Normal	5030 (98.2)	801 (97.4)	97
With malformations	93 (1.8)	21 (2.4)	3.0

- Smaller follow up studies at 6 months to 9 years for bromocriptine and 12 years for cabergoline show no increase in mental or physical disabilities
- DA throughout pregnancy limited data, but no increased adverse effects
  - ~100 cases for bromocriptine
  - 15 cases for cabergoline

Molitch. European Journal of Endocrinology (2015) 172, R205–R213

Effects of pregnancy on prolactinoma

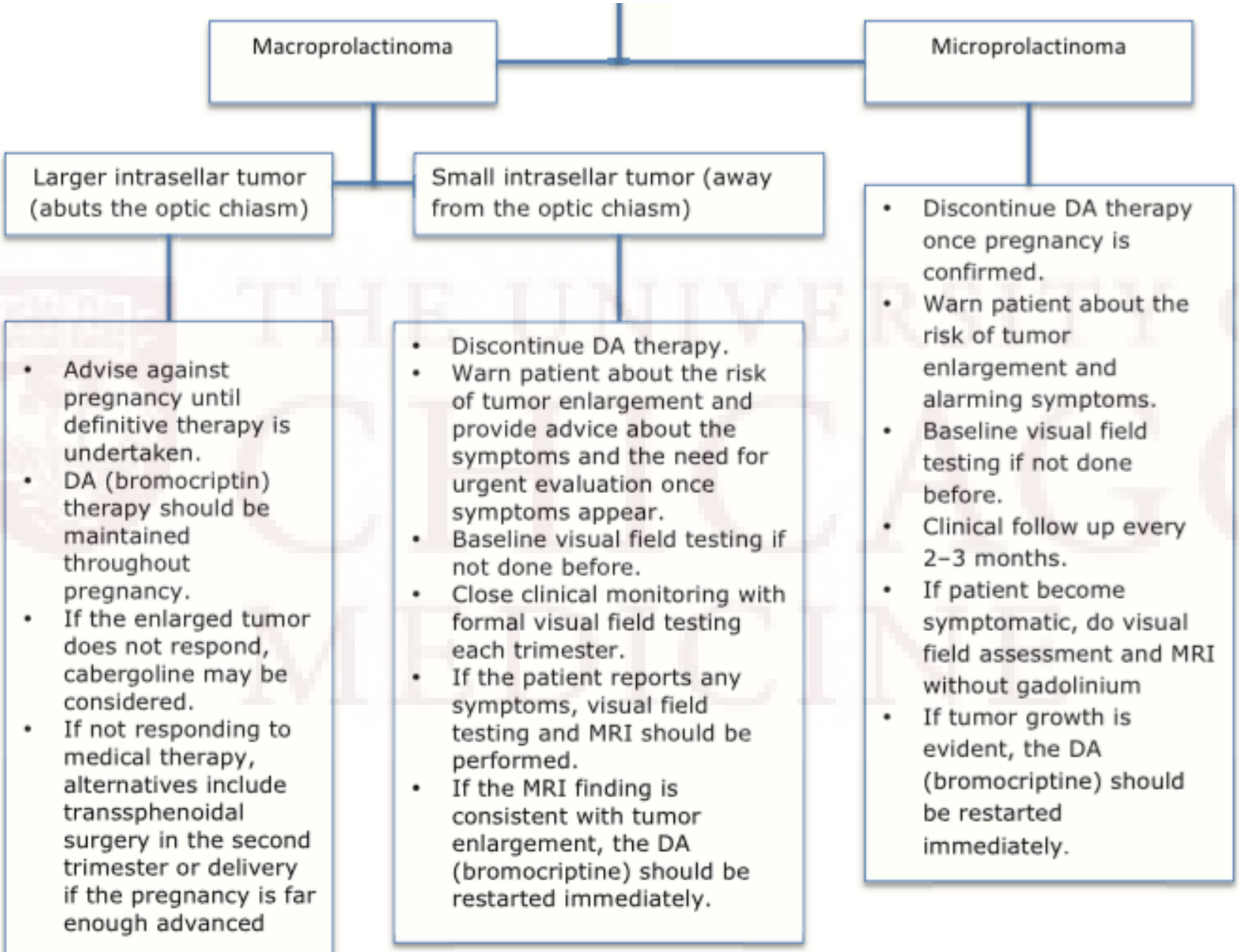
- Estrogen→lactotroph hyperplasia→increased prolactin ostensibly to prepare for lactation
- Pituitary volume increases in size beginning in the second month of gestation and peaks 1 week postpartum
- Peak height of nearly 12 mm
- Risk of ***symptomatic*** tumor enlargement during pregnancy (e.g. progressive HA, visual field deficit) is low and is size-dependent
  - Microprolactinoma: 2.4%
  - Macroprolactinoma (>10 mm): 21.0% →Risk reduced to 4.7% with prior treatment
- Baseline MRI prior to pregnancy should be obtained
- Prolactin levels do not always correlate with tumor growth so monitor clinically (without measuring prolactin levels) during pregnancy
- Treatment recommendations for symptomatic tumors:
  - 1) Reinstitution of DA agonist usually successful
  - 2) Surgery prior to delivery is rarely required
- Measure prolactin levels 2 months after delivery or cessation of nursing

Molitch. European Journal of Endocrinology (2015) 172, R205–R213

Risk of ***symptomatic*** tumor enlargement during pregnancy

Microadenomas		Macroadenomas		Macroadenomas with prior treatment	
Total	No. enlarged	Total	No. enlarged	Total	No. enlarged
85	5	46	20	70	5
246	4	45	7	46	2
26	3	4	2	5	0
8	1	1	0	4	0
54	0	4	4	0	0
22	2	3	1	2	0
16	0	0	0	0	0
5	0	3	1	0	0
48	1	30	11	21	0
56	0	29	0	0	0
45	2	15	3	0	0
47	0	34	0	0	0
76	0	10	0	0	0
30	0	14	1	0	0
764	18 (2.4%)	238	50 (21.0%)	148	7 (4.7%)

Molitch. European Journal of Endocrinology (2015) 172, R205–R213



Almalki et al. Frontiers in Endocrinology (2015) Vol 6. Article 85.

Clinical update

- OBGYN:
  - Steroids given for fetal lung maturity
  - C-section scheduled as outpatient in 2 days due to concern for increased intracranial pressure with labor and history of possible hemorrhage into pituitary mass
- Ophthalmology:
  - Visual field exam stable over 24 hours
- NSGY:
  - Transsphenoidal hypophysectomy one week after delivery
- Re: DA agonist:
  - Discussed possible use of cabergoline or bromocriptine but patient desired breast feeding and given short time frame for surgical intervention did not elect to use these

Continued clinical course

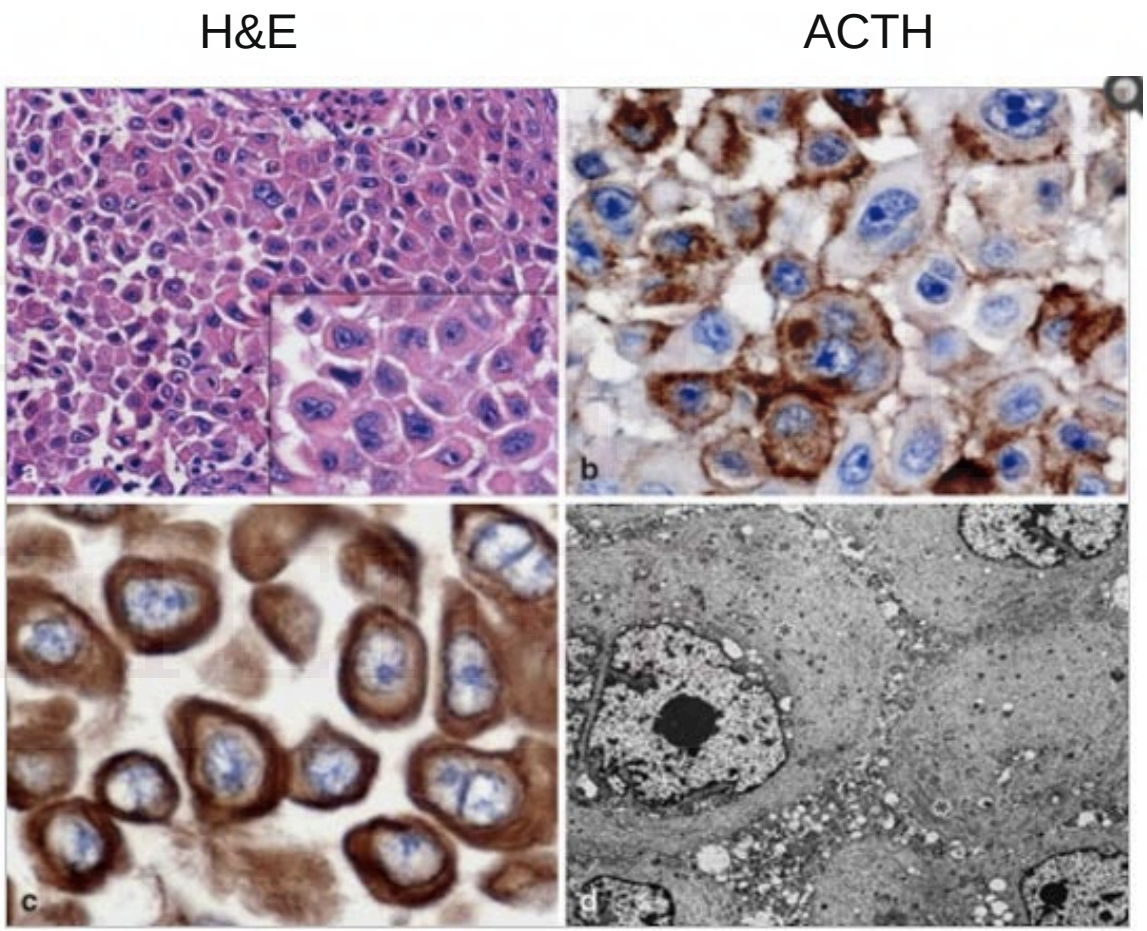
- Uncomplicated C-section with health baby girl
  - Unfortunately, milk production suppressed; unclear etiology but possibly related to perioperative stress dose steroids and surgical stress
- Transsphenoidal hypophysectomy 1 week later
  - Near-total resection (~80%)
  - Operative report : Large mass with necrosis eroding into bone and likely cavernous sinus, possibly encasing carotid artery on R.
  - Post-operative course complicated by persistent DI, discharged on DDAVP 0.5 mg bid
  - Also received stress dose steroids and was discharged on hydrocortisone replacement

Surgical Pathology Report

- *Final Pathologic Diagnosis*
  - *Pituitary*
    - *ACTH-Expressing Pituitary Adenoma, WHO Grade I*
- *Comment*
  - *Sections show disruption of the lobular architecture of the adenohypophysis by a monomorphic proliferation of neuro-endocrine type cells, consistent with pituitary adenoma. Reticulin stains performed on block A2 and B1 confirm the distorted adenohypophyseal architecture.* ***Immunohistochemical stains show that the neoplastic cells are diffusely positive for synaptophysin and CAM5.2, focally positive for ACTH,*** *and negative for Prolactin, GH, FSH, and LH. The Ki-67 proliferation index is approximately 1%.* ***The CAM5.2 immunostain also shows numerous adenhypophyseal cells with Crooke's hyaline change, a morphological change associated with states of cortisol excess****.*
  - *The morpholotical and immunohistochemical features are compatible with ACTH-Expressing Pituitary Adenoma… Although this macroadenoma may represent a silent corticotroph adenoma unassociated with Cushing disease, close clinical follow-up is recommended to exclude Cushing disease.*

Crooke Cell histopathology

- Crooke cell adenomas are very rare ~0.03% of all adenomas
- Typical cytoplasmatic structures include:
  - Hyaline ring of densely arranged microfilaments (A) eosinophilic, hyaline cytoplasm and (C) perinuclear CAM5.2
  - Large lysosomes (lysosmal trapping)
  - Secretory granules around the lysosomes, and at the cell perphery
- Function:
  - 65% hypersecrete ACTH
  - 35% are clinically inactive



Osamura et al. Histochem Cell Biol. 2008 Sep; 130(3): 495–507.

Silent Corticotroph Adenomas

- ***Definition***: Pituitary tumors that are immunoreactive for ACTH but without clinical evidence for Cushing's Disease
  - NO central obesity, moon face, diabetes, hypertension and osteoporosis.
  - May be associated with mildly elevated ACTH (in some cases inactive high-molecular weight ACTH) with normal cortisol levels
- Most commonly present as non-functioning adenomas (NFAs)
- Diagnosis is based on pathology of resected tumor
- Rare:
  - ~10% of pituitary tumors are Corticotroph adenomas
  - SCAs account for:
    - 20% of all corticotroph adenomas
    - 3-19% of NFAs
- Two Types of SCAs:
  - Type I: 68% SCAs (1.1 % of clinically silent adenomas) – more similar in appearance to functional corticotroph adenomas with dense granules, cytokeratin, PAS+, ACTH+, Tpit+
  - Type II: - chromophobic, lack cytokeratin and have sparse staining for other markers

Cooper. Pituitary (2015) 18:225–231
Raverot et al. European Journal of Endocrinology 163 35–43 (2010).
Saeger et al. European Journal of Endocrinology 156 203-216 (2007).

SCAs are more aggressive than NFAs

- Pre-operatively similar in aggressiveness to NFAs
- Post-operatively increased morbidity compared to NFAs
  - More frequent post-operative hypopituitarism
  - Earlier recurrence and more frequent multiple recurrence compared to NFAs (6% at 3 years)
    - Type I 34%
    - Type II 10%
  - Transformation to Cushing's disease is possible
- Surgery is the primary treatment modality (by default) but frequently additional modalities used due to tendency to recur
  - Stereotactic Radiosurgery
  - Somatostatin Analogs (e.g pasireotide)
    - 200 X higher expression of the somatostatin receptor than NFAs
  - Temozolomide (alkylating agent) has been used anecdotally (20-25 cases reported) with some stabilization of tumor size, but frequent progression
  - Bevacizumab (VEGF inhibitor) has been reported for SCA carcinoma with some stabilization of tumor size

Table 1 Case series of SCAs

Reference	n	NFA control group	Cavernous sinus invasion	Preoperative hypopituitarism	Recurrence rate	New onset postoperative hypopituitarism	Significant findings
Scheithauer 2000 [49]	23	No	7/23 (30 %)	14/23 (61 %)	7/13 (54 %)	12/22 (55 %)	More aggressive
Webb 2003 [59]	27	No	13/25 (52 %)	3/27 (11 %)	10/27 (37 %)	9/27 (33 %)	More aggressive
Bradley 2003 [5]	28	Yes	n/a	n/a	9/28 (32 %)	n/a	No difference in recurrence rate or time to recur between groups
Lopez 2004 [29]	12	No	n/a	4/12 (33 %)	0/12	2/12 (17 %) adrenal insufficiency	Short follow-up
Baldeweg	15	No	6/15	n/a	5/15 (33 %) recurred	n/a	4 transformed to CD
Pooled results	332		103/241 (43 %)	92/225 (41 %)	84/309 (27 %)	37/92 (40 %)	
Cho 2009 [8]	28	Yes	11/28 (39 %)	9/22 (41 %)	7/28 (25 %)	7/18 (57 %) adrenal insufficiency	More multiple recurrences in SCAs; younger age in SCAs
Cooper 2010 [10]	25	Yes	7/17 (41 %)	5/13 (38 %)	10/17 (59 %)	7/13 (54 %)	Median time to recur 3 years in SCAs cf to 8 yrs in NFAs
Alahmadi 2012 [2]	20	Yes	6/20 (31 %)	3/20 (13 %)	3/20 (14 %)	n/a	Similar recurrence rates to NFAs
Ioachemiscu 2012 [19]	33	Yes	15/33 (46 %)	25/33 (76 %)	8/17 (47 %) growth of residual; 2/16 (13 %) de novo recurrences	24/31 (77 %) unchanged from preoperative	Higher preoperative hypopituitarism in SCAs; 7 SCAs more aggressive (21 %) vs 14 % NFAs (NS)
Jahangiri 2013 [20]	75	Yes	16/54 (30 %)	29/75 (54 %)	16/60 (27 %) recur	n/a	More cavernous sinus invasion and recurrences in SCAs
Pooled results	332		103/241 (43 %)	92/225 (41 %)	84/309 (27 %)	37/92 (40 %)	

Continued clinical course

- Repeat imaging stable – planning for monitoring Q 6 months given residual tumor, followed by NSGY
- Visual field defects resolved
- HA intermittent, possibly related to computer work; undergoing evaluation with Neurology
- Diabetes insipidus managed with DDAVP
- Planned evaluation for subclinical Cushing's given pathology (no clinical evidence of hypercortisolism) but patient has not yet followed through with testing.