THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

AT THE FOREFRONT OF MEDICINE®

48 y.o Female with Pituitary Lesion

Endorama

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THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

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I have no relevant financial relationships with any commercial interests

OBJECTIVES

- Work up for pituitary lesions
- Unusual differential diagnosis of sellar masses
- Acromegaly diagnosis work up
- Acromegaly management

HPI

- 48 yo female with PMH of Pseudotumor cerebri, HTN, migraines and possible demyelinating disorder
- Endo outpatient visit for pituitary macroadenoma
- Referred by Neurology after incidental macroadenoma found on MRI done for headache work up

PMH:

- CNS demyelinating disease
- Hypertension
- IIH (idiopathic intracranial hypertension)
- Migraine
- OSA on C-PAP
- Schizoaffective disorder

PSH:

- C-Section
- Hx tonsillectomy/adenoidectomy
- Hx tubal ligation

PFH:

- Pulmonary hypertension Mother
- Hypertension Mother
- Diabetes Brother
- Heart Failure Mother
- Diabetes - Type 2 Father
- Diabetes Maternal Grandfather

SH:

- Smoking status: *former Smoker, 15 PPD*
- Alcohol use: *rarely, on holidays*
- Drug use: *prior Marijuana, cocaine user ~20 years ago*

Meds:

- Acetazolamide-SR (DIAMOX SEQUELS) 500 mg Oral cpER
- AmLODIPine (NORVASC) 10 mg Oral tablet
- Cyclobenzaprine (FLEXERIL) 10 mg Oral tablet
- Melatonin 3 mg by Oral route
- Nortriptyline (PAMELOR) 25 mg Oral capsule
- Rizatriptan (MAXALT-MLT) 10 mg Oral PRN
- TraMADol (ULTRAM) 50 mg Oral tablet

REVIEW OF SYSTEMS

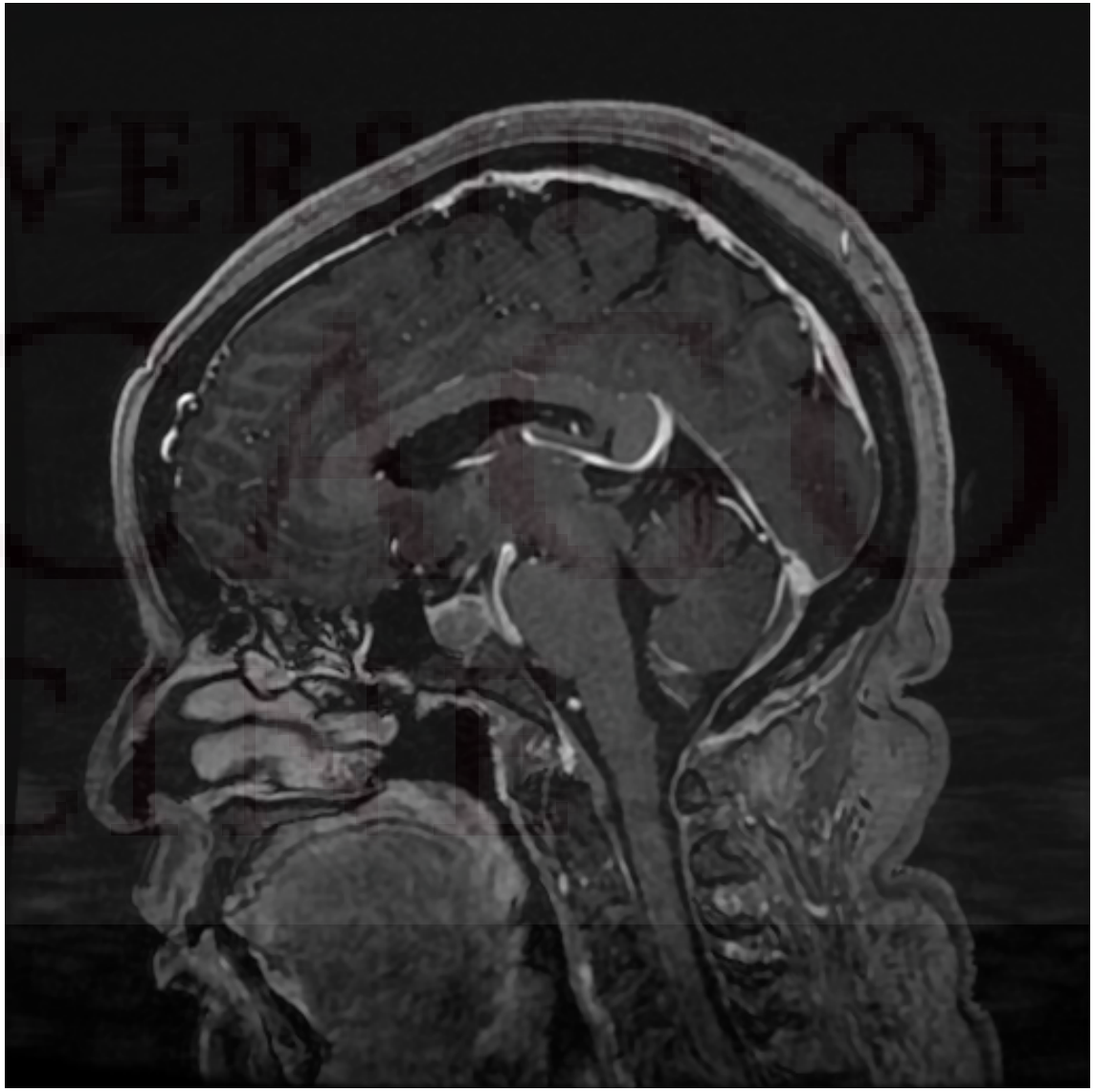
- Constitutional: Positive for **fatigue** and **unexpected + weight change**
- Eyes: Positive for visual disturbance **(blurry)**
- Respiratory: Negative
- Cardiovascular: Negative
- Gastrointestinal: Negative
- Endocrine: Positive for heat intolerance **(hot frequently)**
- Neurological: Positive for dizziness and headaches
- Psychiatric/Behavioral: no SI

PHYSICAL EXAM

- Constitutional: She is oriented to person, place, and time
  obese
- HENT:
  No acanthosis
  ?mild frontal bossing
- Cardiovascular: Normal rate, regular rhythm and normal heart sounds
- Pulmonary/Chest: Effort normal and breath sounds normal
- Abdominal: Soft. Bowel sounds are normal. She exhibits no distension
  No striae
- Musculoskeletal: She exhibits no edema
- Neurological: She is alert and oriented to person, place, and time
- Skin: Skin is warm
- Psychiatric: She has a normal mood and affect. Her behavior is normal

MRI BRIAN WO

- The pituitary gland measures approximately 12 mm in height and appears enlarged
- A nonenhancing component within the pituitary gland measures approximately 15 mm in width and 12 mm in height
- The pituitary stalk is slightly tilted towards the right



LABS

How would you proceed?

Endocrine labs	
Prolactin	19.4 (2.3-26.7)
FSH	7.1
LH	5.1
ACTH	24 (6-50)
TSH	1.02
IGF-1	587 (52-328)

Glucose, Ser/Plasma	108 *
Sodium	143
Potassium, Ser/Plasma	3.5
Chloride	115
Carbon Dioxide	15
Anion Gap	13
BUN	12
Creatinine	0.9
GFR Estimate (Calc)	67 *
Calcium	9.2

WBC	11.6
RBC	3.81
Hemoglobin	10.7
Hematocrit	34.0
MCV	89.2
MCH	28.1
MCHC	31.5
RBC Dist Width	15.4
Platelet Count	295
Mean Platelet Volume	10.3

HbA1c (POC)	5.2

HISTORY – CONTINUED

She noted:
- Enlargement of her face
- She has gone up one shoe size in the past two years
- Her rings are not coming off as easily
- She has gained 30-40 pounds the past two years which she attributes to discontinuation of tobacco use
- She denies any breast discharge
- She has regular monthly cycles and is not on any hormonal contraception

Patient had an ophthalmology visit:
- Humphrey Visual Field was normal. She complains of blurry vision and sunlight bothers her

LABS

Endocrine labs	
Prolactin	19.4 (2.3-26.7)
FSH	7.1
LH	5.1
ACTH	24 (6-50)
TSH	1.02
IGF-1	587 (52-328)

IGF1 LC MS	459 ^	44 - 227 ng/mL

Cortisol	7.0

Thyroxine, Free	1.00 *	0.85 *
Thyrotropin		0.66 *

Glucose, Ser/Plasma	108 *
Sodium	143
Potassium, Ser/Plasma	3.5
Chloride	115
Carbon Dioxide	15
Anion Gap	13
BUN	12
Creatinine	0.9
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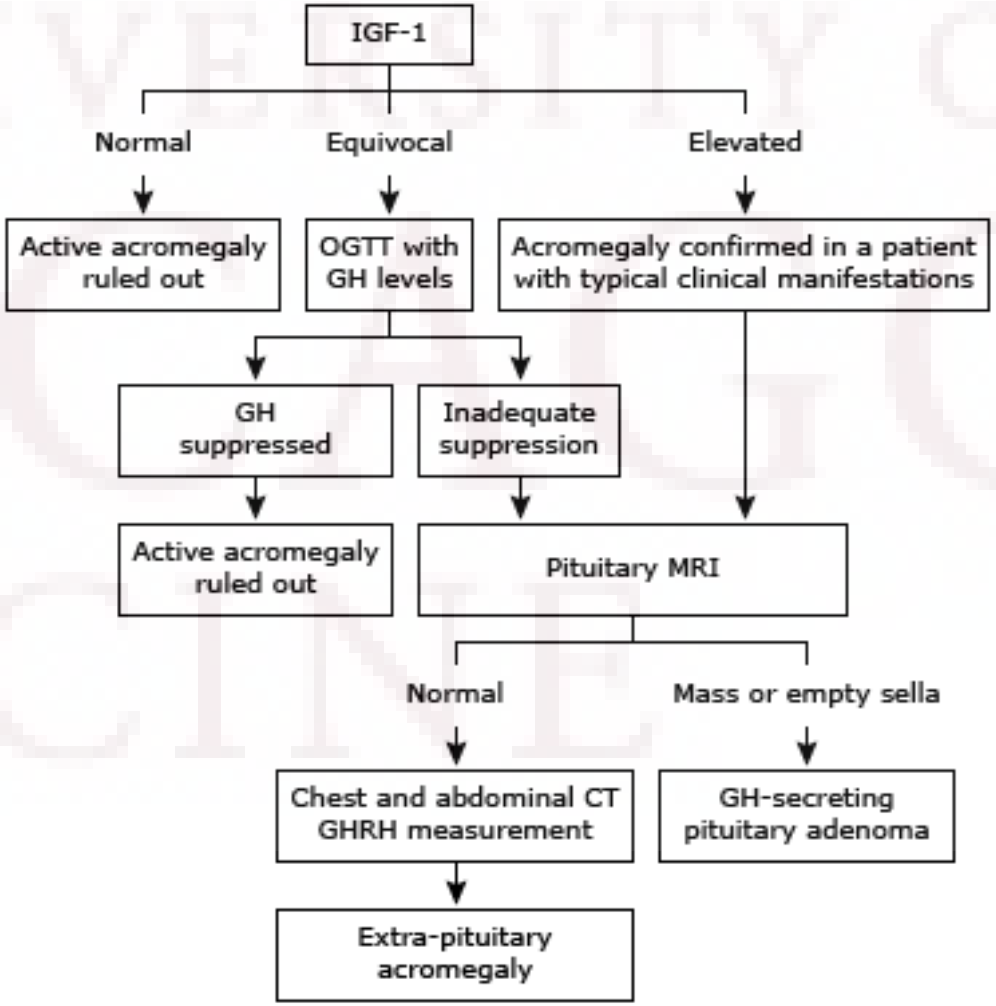
ACROMEGALY

Algorithm for the diagnosis of acromegaly

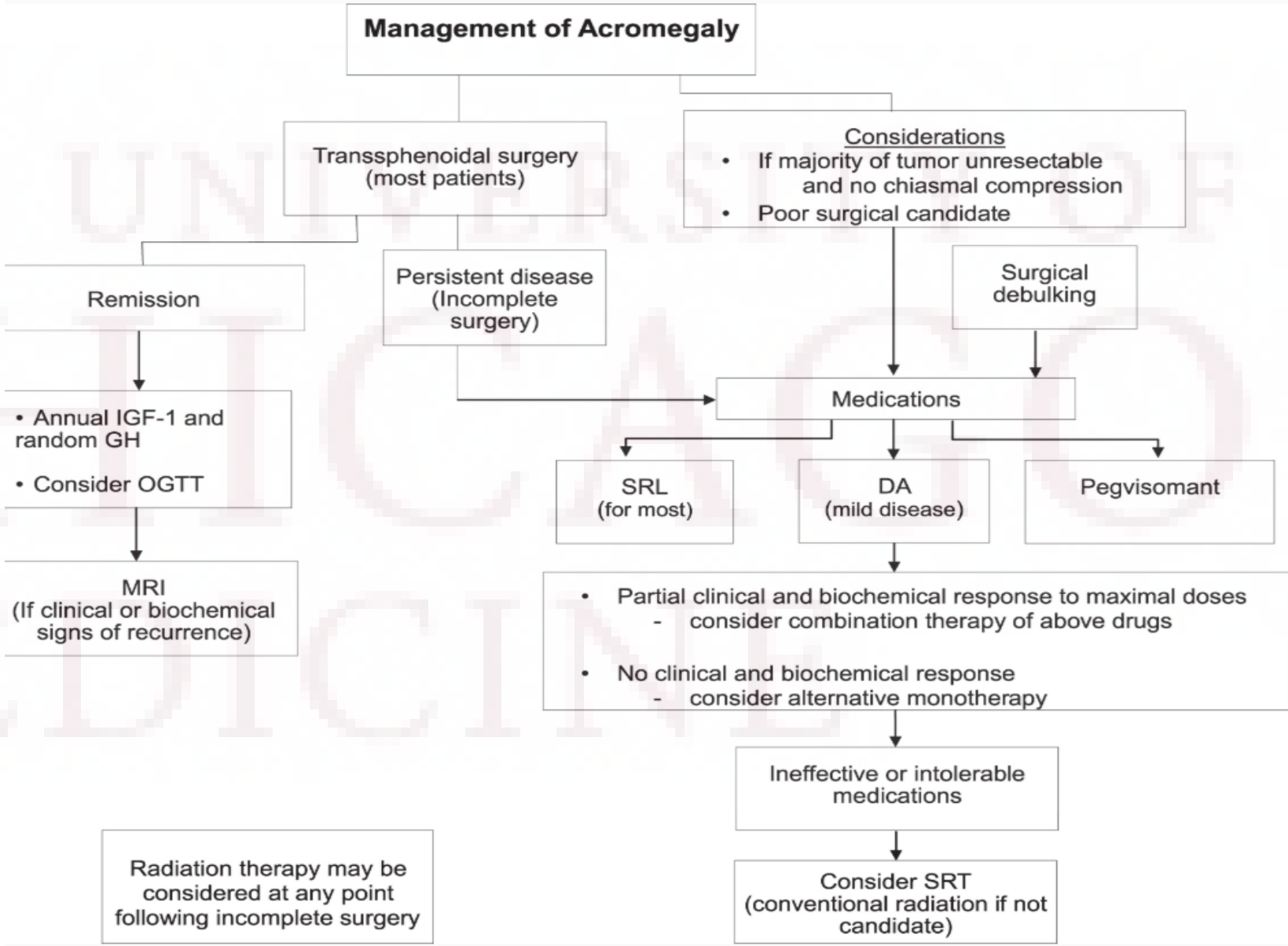


Goals of management:

- Target goal of an age-normalized serum IGF-1 value, which signifies control of acromegaly

- Random GH < 1.0 µg/L as a therapeutic goal, as this correlates with control of acromegaly

Surgery Indication: transsphenoidal surgery as the primary therapy in most patient



Katznelson et al., J Clin Endocrinol Metab. 2014

BACK TO THE PATIENT

- Undergone endoscopic transsphenoidal resection of pituitary macroadenoma

Pathologic Diagnosis:

- "Pituitary tumor" (part B): Gangliocytoma
- "Dura" (part A): Fragment of dense connective tissue with focal nests of anterior pituitary parenchymal cells

“Abundant fibrillary "neuropil-like" stroma and within that scattered focally clustered dysplastic ganglion cells. +stains for synaptophysin and neurofilament ➔ gangliocytoma

- Lacks convincing reactivity for prolactin, growth hormone, TSH, and ACTH

“Most sellar gangliocytomas are associated with areas exhibiting more typical pituitary adenoma morphology. In this particular case, though, no adenoma features are seen in the available material. Cases of mixed adenoma / gangliocytoma are often associated with endocrinopathy, most commonly acromegaly. There is less data on cases lacking a clear adenoma component. “

UNUSUAL SELLAR/SUPRASELLAR REGION MASSES

- >7000 sellar/suprasellar region masses at Pituitary Tertiary Care Centers.

Common lesions	rare lesions (collectively 6.0%)
Pituitary adenomas (84.6%),	mixed pituitary adenoma-gangliocytoma
craniopharyngiomas (3.2%),	Large B Cell Lymphomas of the
cystic nonneoplastic lesions (2.8%)	Neurosarcoidosis Mass
inflammatory lesions (1.1%)	Granulomatosis With Polyangiitis
meningiomas (0.94%)	CLL Within a Pituitary Adenoma
metastases (0.6%),	plasmacytomas myeloid sarcomas
chordomas (0.5%).	- T cell lymphoblastic leukemia/lymphoma - hemangiopericytoma - primary sella region choroid plexus papillomas - Small cell gangliocytoma - cavernous angiomas - abscesses within adenomas - intrasellar paragangliomas - atypical rhabdoid tumors of the sella, - fibrosarcoma of the Sella

Abushamat et al., Jou. of Neurop. & Exper. Neuro., 2019

POST SURGERY

- She was placed on hydrocortisone postoperatively
- Still reports fatigue, 15 lbs weight gain and feeling cold a lot
- She has regular monthly cycles and is not on any hormonal contraception
- Headaches resolved postoperatively

- Post surgery:

IGF1 LC MS	305 ^	44 - 227 ng/mL

What would you do?

Repeat at O/P visit:

IGF1 LC MS	458 ^	44 - 227 ng/mL

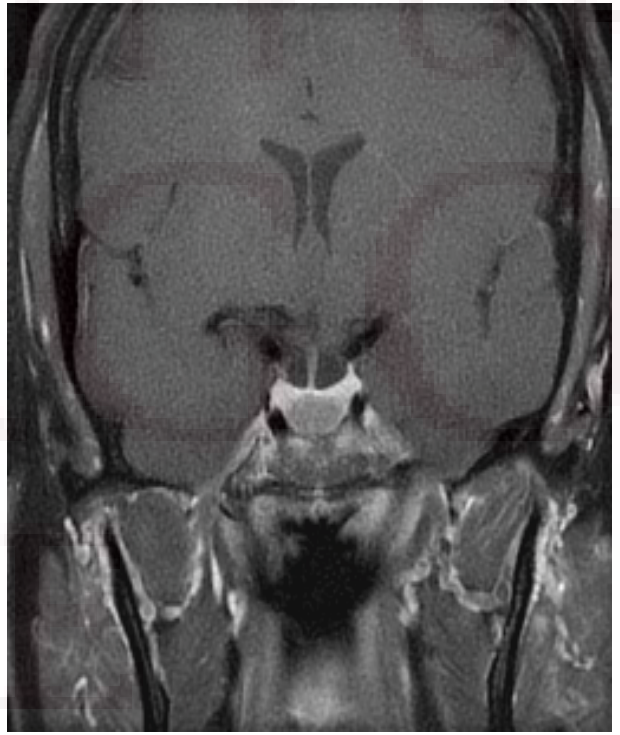
IGF-1 ASSAYS

Falsely elevated IGF-1
Adolescence
Pregnancy
Hyperthyroidism (mild elevation)
IGF-1 assay problems
Early postoperative period

Freda et al., Clin Endocrinol (Oxf). 2009

MRI PIT. POST OPERATIVE

- There are postoperative findings related to transsphenoidal surgery
- Hypoenhancing mass in the pituitary gland that measures up to 12 mm
- No mass effect upon the anterior visual pathway structures or cavernous sinuses
- The pituitary stalk is intact



What would you do next?

FROM GUIDELINES

- Microscopic or endoscopic transsphenoidal microsurgery results in an initial remission rate 85% for microadenomas and 40 – 50% for macroadenomas
- Five-year disease recurrence rates range from 2 to 8%
- Repeat surgery can be considered in a patient with residual intrasellar disease following initial surgery

Katznelson et al., J Clin Endocrinol Metab. 2014

CONFIRMATION LABS

IGF1 LC MS	458 ^		44 - 227 ng/mL

Oral glucose tolerance test

	4 11/20/2018 0932	3 11/20/2018 0932	2 11/20/2018 1135	1 11/20/2018 1135
PROVOCATIVE ENDOCR...				
Elapsed Time (Endo...	*0*	*0*	*120*	*120*
Growth Hormone, St...		*1.65*		*1.42*
Insulin Stimulated	*56.1*		*186.8*	

"An inability to suppress GH secretion to < 1 µg/L during 2 hours after an oral glucose load is diagnostic of acromegaly"

POST OPERATIVE (2) PATHOLOGY

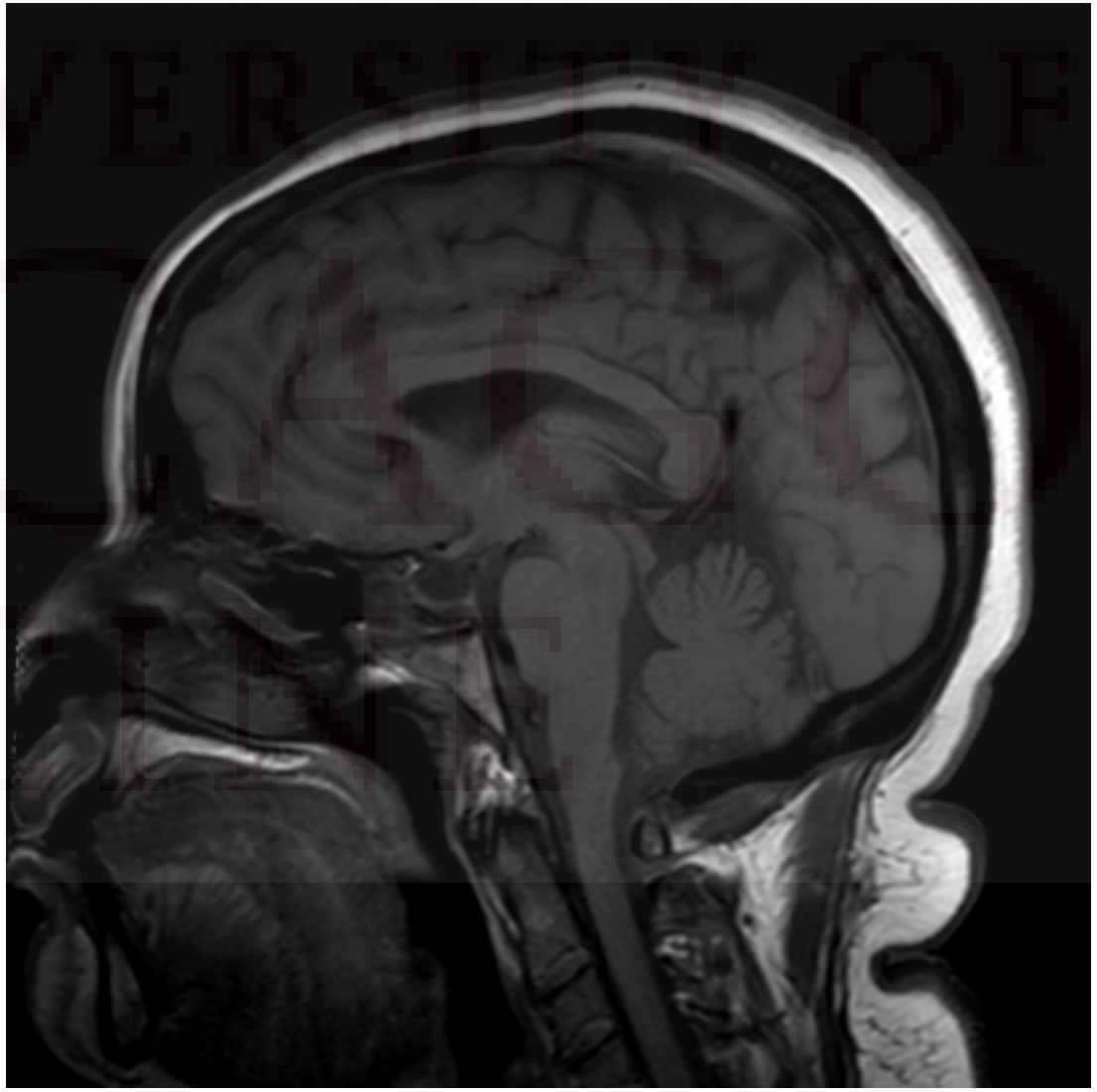
- Final Pathologic Diagnosis:

  Gangliocytoma with areas of conventional Growth Hormone positive pituitary adenoma

BRAIN MRI POST OP-2

IMPRESSION:

- Expected postoperative findings related to recent transsphenoidal surgery
- Significant interval decrease in size or perhaps complete resolution of previously seen hypoenhancing pituitary gland soft tissue



POST OPERATION 2

- Two months after:
  - She noted her hands are less enlarged, and rings are falling off
  - She was placed on LT4 25 mcg daily
  - She has regular monthly cycles
  - Is due for IGF-1 testing

SELLAR GANGLIOCYTOMAS

- Gangliocytomas originating in the sellar region are rare; most are tumors composed of gangliocytic and pituitary adenomatous elements

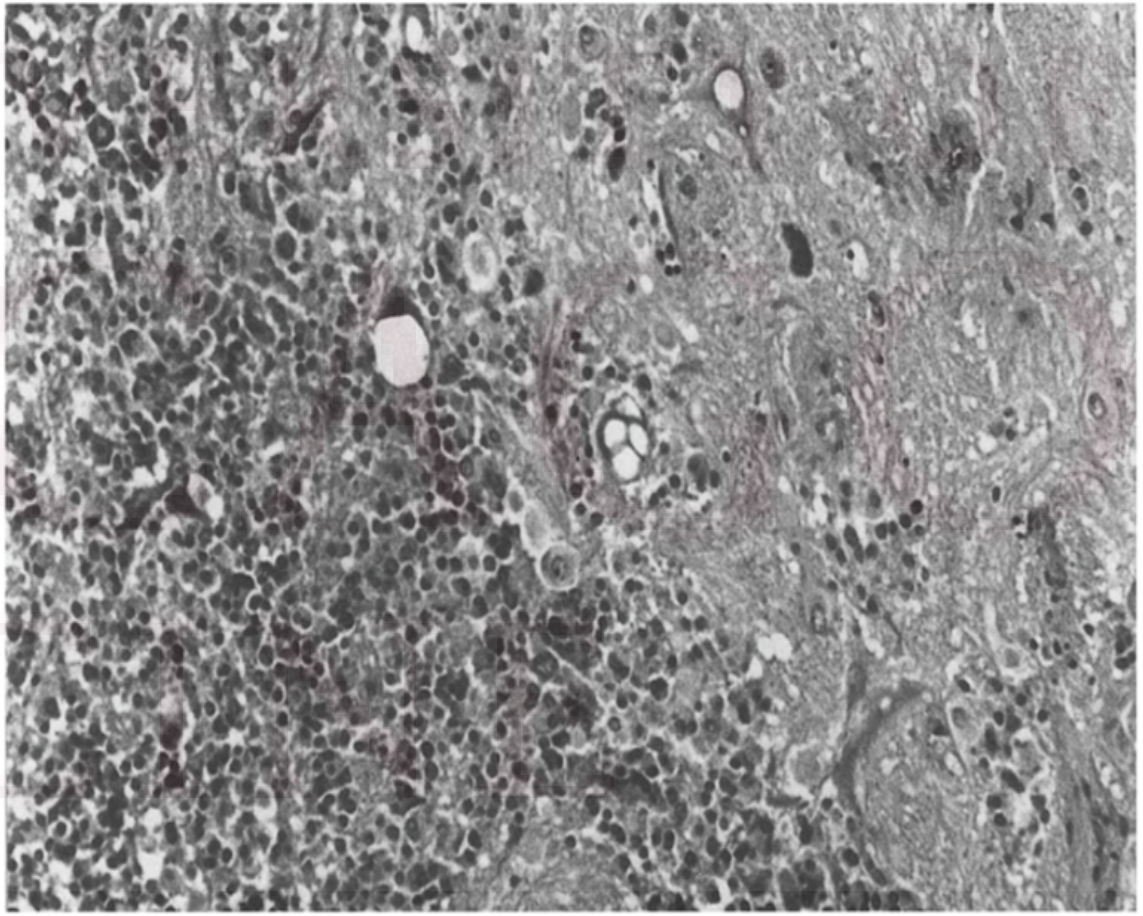
Case #	Age/Sex	Clinical Presentation	Laboratory Data	Adenoma Type
1	46/F	Acromegaly	↑IGF-1	SG-GH
2	58/F	Acromegaly	↑ IGF-1	SG-GH
3	27/F	Acromegaly, amenorrhea, and galactorrhea	↑ IGF-1, ↑PRL	SG-GH
4	33/F	Incidental finding work-up for headaches; no acromegaly signs	nl IGF-1	SG/DG-GH
5	44/M	Acromegaly	↑ IGF-1	SG-GH
6	40/M	Acromegaly, headaches, CHF	↑ IGF-1	SG-GH
7	52/F	Headaches, visual disturbances; no acromegaly signs	↑ IGF-1	SG-GH
8	44/F	Incidental finding after MVA; no acromegaly signs	↑ IGF-1	SG-GH
9	63/F	Incidental finding on sinuses MRI; no acromegaly signs	nl IGF-1	SG-GH
10	38/M	Acromegaly	↑ IGF-1	SG-GH

- Ganglionic cells expressing neuronal-associated proteins the acidophilic lineage transcription factor Pit-1, suggesting a Rathke pouch origin for these ganglionic elements
- There is not enough data in the literature to draw firm conclusions of tumor behavior that would differ from the ordinary SG-GH

Lopes et al., Am J Surg Pathol. 2017

STUDY 2

- Three patients with sellar lesion consisting of a gangliocytoma and a pituitary adenoma:
  - two with acromegaly
  - one with Cushing's disease
- Gangliocytoma demonstrated GHRH and CRH
- ➔Gangliocytomas may have triggered the development of pituitary adenoma via paracrine secretion of the hypothalamic releasing hormones
- The resulting pituitary adenomas were then the source of the elevated hormones responsible for the hormonal syndromes

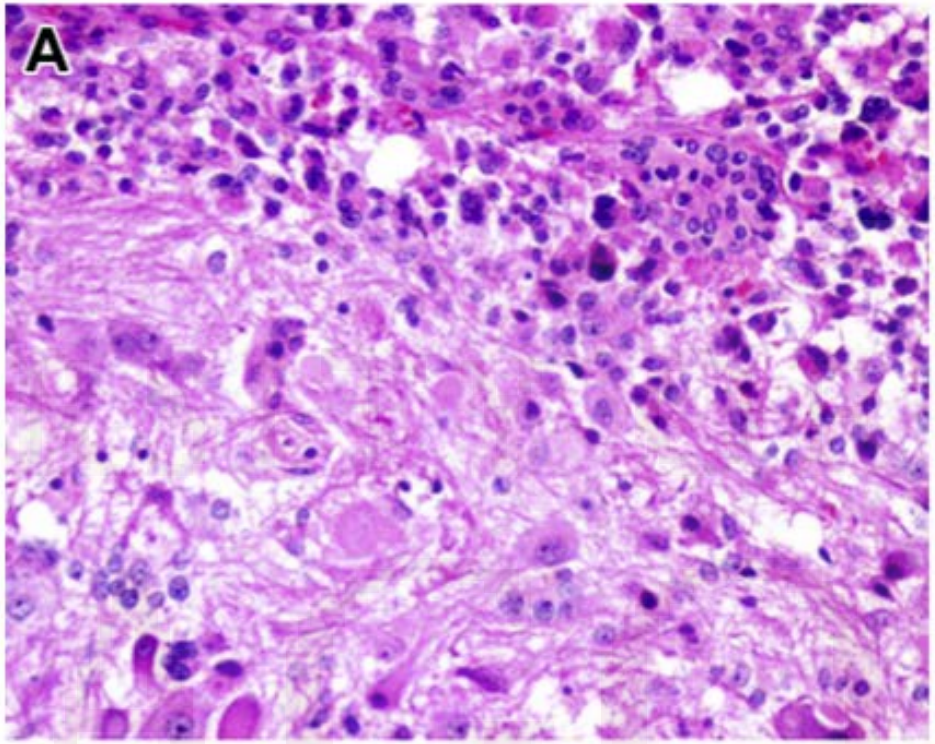


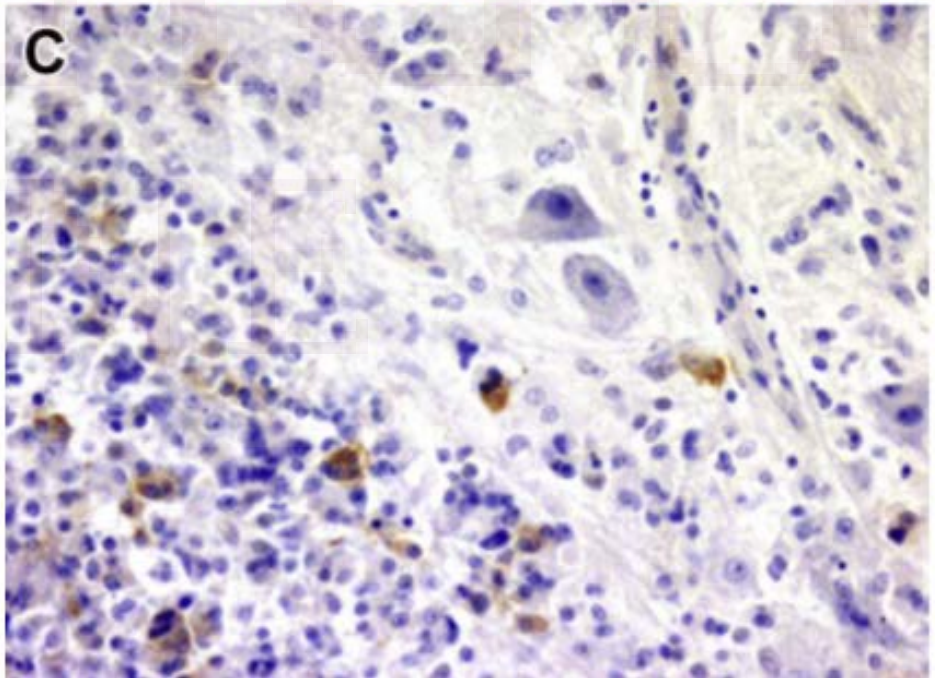
Adenoma with relatively small, densely arranged cells (left) and GHRH-gangliocytoma with large cells (right)

Saeger et al., Virchows Arch. 1994

STUDY 3

- Patients diagnosed with a combined sellar mixed ganglio/adenoma (MGA) between 1993 and 2016
- 16 patients were diagnosed with MGA
- Median age 42 years
- All were female
- Literature search of MGA cases previously reported:
  - 75% of patients with MGA had evidence of a hypersecretory pituitary adenoma
  - Acromegaly (54%)
  - Cushing disease (11%)
  - Prolactinomas (10%)





Shepard et al., World Neurosurg. 2017

STUDY 4

- Sellar tumors (n=4317) in the pathology archives (2006 and 2017) were reviewed
- Retrieved 20 consecutive cases of sellar mixed gangliocytoma-pituitary adenoma
- Preoperative endocrine examination showed elevated IGF-1 in nine (45.0%)
- All 20 had no recurrence

Characteristics	Number	Percentage	Characteristics	Number	Percentage
Gender			Involvement		
Female	94/120	78.3	Suprasellar region	46/82	56.1
Male	26/120	21.7	Cavernous sinus	29/82	35.4
Age (years; mean ± SD)	44.8 ± 11.4		Sphenoid sinus	10/82	12.2
Symptoms			Immunohistochemistry		
Headache	36/115	31.3	GH	101/136	74.3
Visual disturbance	35/115	30.4	PRL	74/136	54.4
Hypersecretion of GH	71/115	61.7	TSH	5/136	3.7
Hypersecretion of PRL	28/115	24.3	ACTH	12/136	8.8
Hypersecretion of ACTH	8/115	7.0	NAEM	9/136	6.6

Characteristics of mixed gangliocytoma-pituitary adenomas reported in previous literatures

- Both gangliocytoma and pituitary adenoma are classified as benign entities corresponding to WHO grade I
- Mixed gangliocytoma-pituitary adenomas are also considered with a benign nature

Young et al., Acta Neurochir (Wien). 2018

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THANK YOU

Questions/comments?