A 56-YEAR OLD MALE WITH HEADACHES AND VOMITING

HISTORY OF THE PRESENT ILLNESS

56-year old male, with complicated medical history, including extensive cardiac disease and chronic kidney disease, presenting with:

One month history of low grade, tension-type headache; acute worsening with sudden-onset "smashing" right-sided temporal headache on the night prior to admission.

Headaches associated with nausea and recurrent emesis. No relief with Tylenol #3 or NSAIDS.

No precipitating trauma.

No associated vision changes, confusion, lethargy, rhinorrhea, or aura.

PAST MEDICAL & SURGICAL HISTORY

Non-Ischemic Dilated Cardiomyopathy
Orthotopic Heart Transplant 2005, complicated by cardiac allograft vasculopathy
Re-transplant March 2013; s/p biV-AICD

- Mycophenolate mofetil
- Tacrolimus
- Predisone 5 mg

Chronic Kidney Disease
LECT-2 amyloidosis

Anemia

- Erythropoietin
- Cyanocobalamin
- Folate
- Ferrous sulfate

Hypertension

- Diet-controlled after transplant

Dyslipidemia

- Pravastatin

Barrett's Esophagus

- Esomeprazole

Depression

- Citalopram

SOCIAL AND FAMILY HISTORY

Lives between US and Mexico
US Citizen since 2007

Lives with wife

Quit tobacco in 2004
No etoh or illicit drug use

Father died in 70s; Cause unknown

Mother alive, healthy, in late 80's

4 brothers, 4 sisters.
1 brother with heart failure, CVA

4 grown children (all with advanced professional degrees) living in Mexico

REVIEW OF SYSTEMS

Constitutional: Denies fevers, chills, hot or cold intolerance. Reports fatigue, 20 pound weight loss (since transplant 6 mos. ago).

HEENT: Denies vision changes including blurriness, loss of peripheral vision or double vision, tinnitus, rhinorrhea, trouble swallowing, neck pain or goiter. Worsening headaches, right molar dental caries worsening headache.

Cardiovascular: Denies chest pain, palpitations or racing heart, syncope, lower extremity edema

Respiratory: Denies difficulty breathing or shortness of breath, cough, or wheezing.

Gastrointestinal: Denies changes in appetite, abdominal pain. Nausea, vomiting, and constipation.

Genitourinary: Denies urinary symptoms. No erectile dysfunction or change in libido.

Musculoskeletal: Diffuse arthralgias and occasional joint swelling in his arms. No changes in shoe, ring finger size.

Neurological: Denies tremors, numbness, tingling, weakness.

Skin: Denies diaphoresis, new rash, changes in hair or nails. New frontal acne.

Psychiatric/Behavioral: Reports depressed mood, anxiety. Wife reports has been more "nervous."

PHYSICAL EXAMINATION

BP 129/83 **P** 92 **T** 36.6 **R** 81 **O2** 96% RA **Wt** 77.5 kg **Ht** 170.2 cm

GENERAL: Oriented to person, place, and time. Well-developed, well-nourished. No acute distress. **Tired appearing.**
HEENT: EOMI. Oropharynx clear. No frontal bossing or macroglossia is evident. There are no gross visual field deficits to confrontation.
NECK: Supple. Thyroid soft. There is no apparent goiter or thyromegaly. No acanthosis nigricans or skin tags are noted.
CV: Regular rate and rhythm. No murmurs, rubs, or gallops are appreciated. No JVD.
RESP: Good respiratory effort, clear to auscultation bilaterally with no wheezes or rales.
ABD: Soft, non-tender, non-distended. Normal bowel sounds present. No hepatosplenomegaly is appreciated. There are no violacieous striae.
GENITOURINARY: No galactorrhea expressed from nipples bilaterally.
MSK: Normal range of motion. No edema. 2+ distal peripheral pulses.
NEURO: No tremors. Normal gait. Normal reflexes with no change in relaxation phase.
SKIN: Skin is warm and dry. **Frontal acne is present.**
PSYCH: Normal mood and affect. Behavior, thought content appear normal.

DIAGNOSTIC EVALUATION

Glucose	105
Sodium	140
Potassium	4.2
Chloride	101
CO2	23
Anion Gap	16
BUN	50
Creatinine	2.3
GFR	30
Calcium	10.0
Albumin	4.1
Total Protein	6.1
T bili	0.5
Alk Phos	29
AST	21
ALT	11

WBC	6.3
HGB	14.2
HCT	43.2
PLT	180

TSH	1.37

CSF Analysis	Total cell count 25 RBC 25 Glucose 75 Protein 44 Bacterial, Fungal, HSV, CMV, JCV, Cryptococcal, AFB cultures Negative

DIAGNOSTIC EVALUATION OF HEADACHES - CT HEAD WO

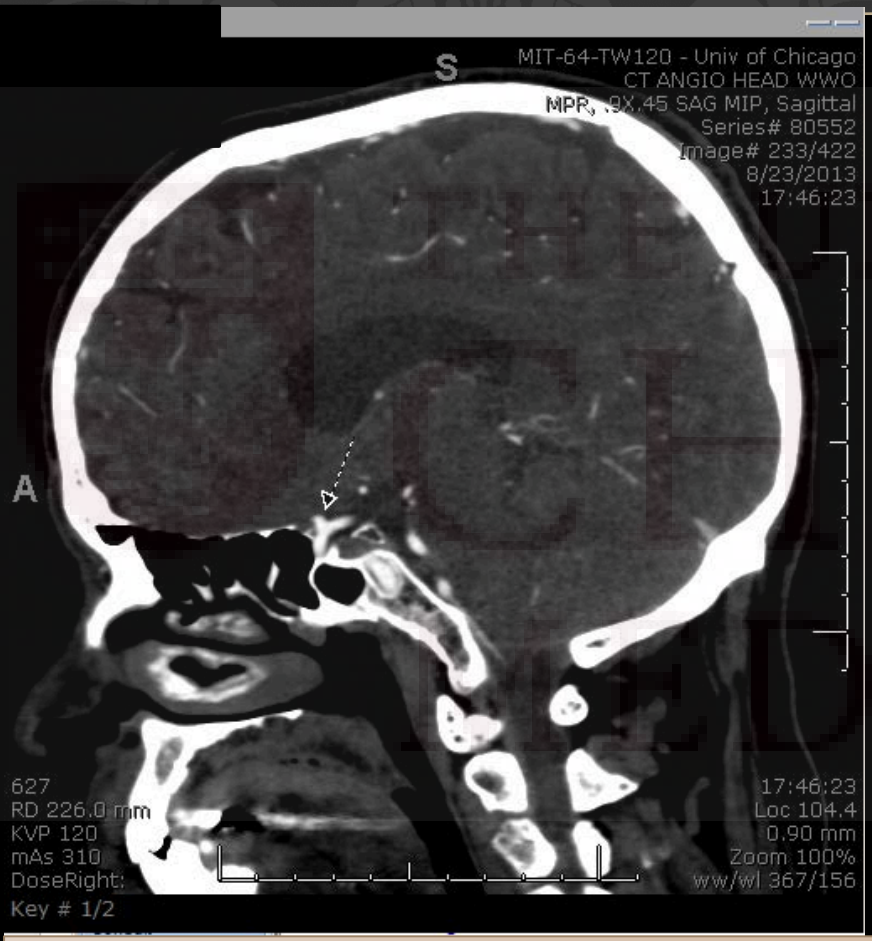
Soft tissue density is demonstrated extending from the left cavernous sinus region into the left sella turcica.

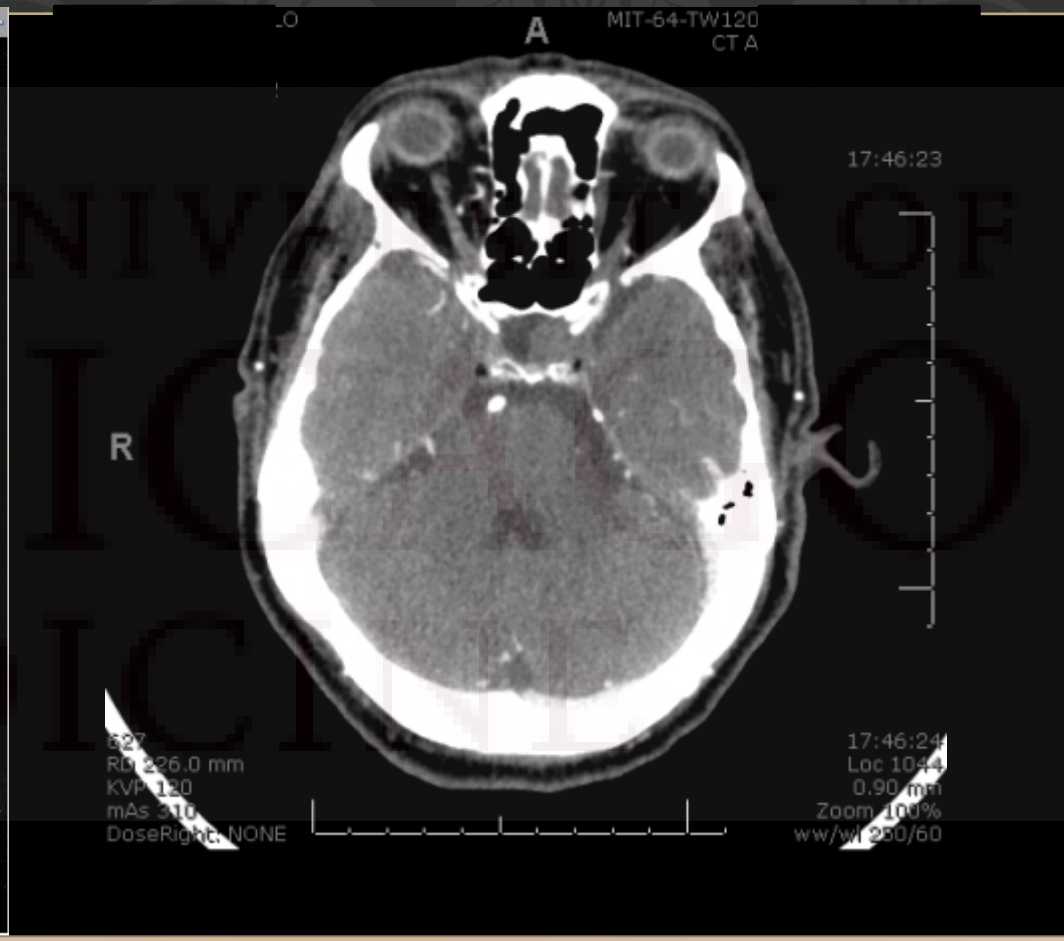
Ddx includes tortuous cavernous portion of internal carotid artery, meningioma, carotid a. aneurysm, or less likely pituitary adenoma.

Further eval with MRI brain/pituitary and MRA wwo is recommended.

Mild small vessel ischemic changes.

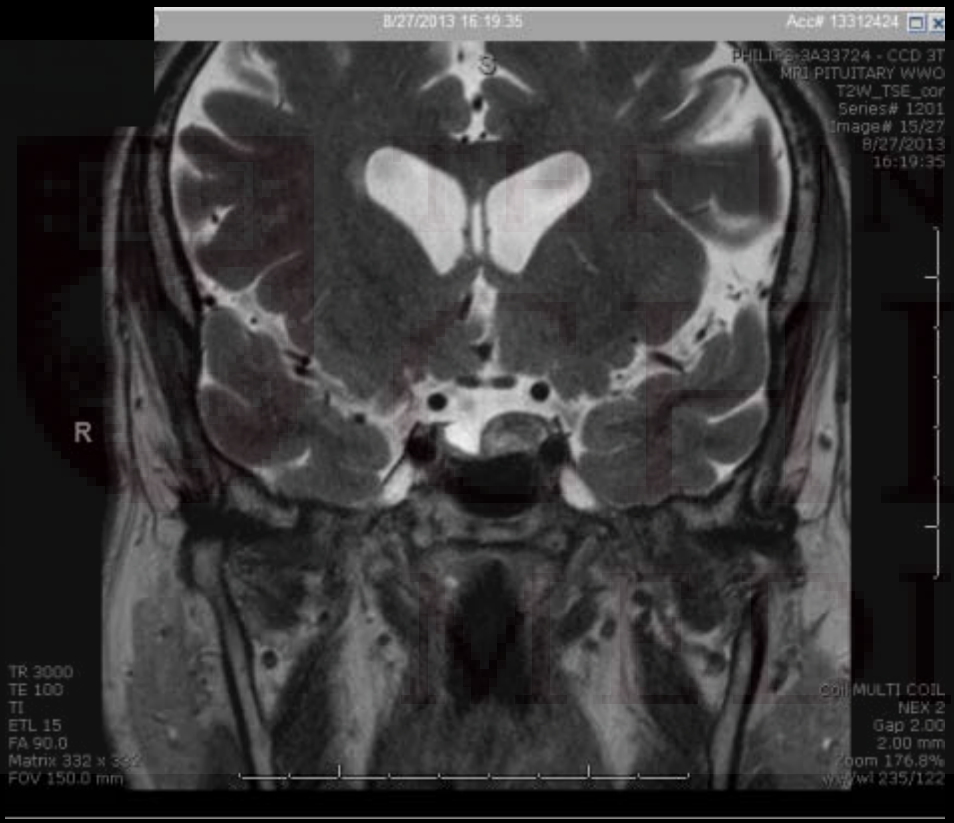
CT ANGIO HEAD WWO

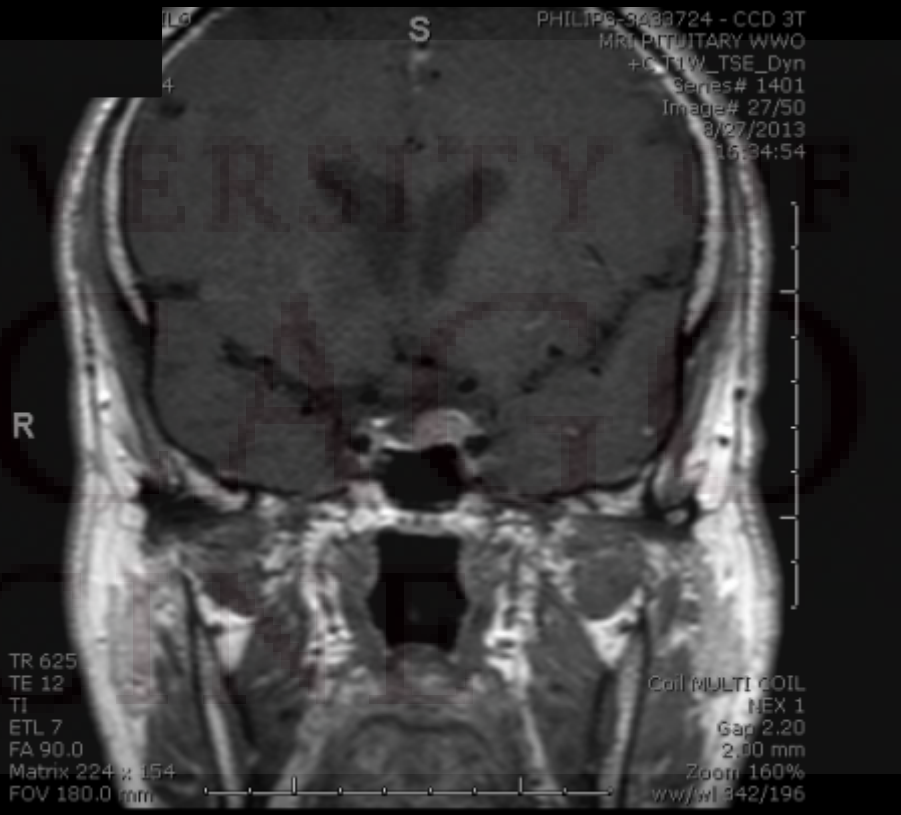




Redemonstration of soft tissue lesion occupying left sella and perhaps left cavernous sinus. Lesion may contact the left ICA, but is not vascular or aneurysmal in nature. The native pituitary gland is not clearly distinguished, and so the relationship of the lesion to the pituitary gland cannot be determined. The differential diagnosis would include meningioma or primary lesion of pituitary. MRI remains only adequate modality to better assess this lesion.

PITUITARY MRI





"The left half of the pituitary is heterogeneous and enlarged in appearance whereas the right half looks like a partial empty sella. It is conceivable that this may represent a microadenoma in the left half of the pituitary possibly associated with empty sella on the right side. An alternative explanation may be there is a different soft tissue mass in the left half of the sella such as a meningioma or another lesion."

BIOCHEMICAL EVALUATION OF PITUITARY AXES

Free Testosterone	97
Total Testosterone	271 Ref Range: 180-800 ng/dL
Sex Hormone Binding Globulin	29 Ref Range: 10-80 nmol/L

FSH	5.1
LH	6.4

Prolactin	14.2 Ref range: 4-15.2 ng/mL

Insulin-Like Growth Factor 1	386 Ref range: 81-225 ng/mL
Insulin-Like Growth Factor Binding Protein 3	6.6 Ref range: 3.4 -6.9
Growth Hormone	1.5 Ref range: 0-4.2ng/mL

TSH	1.37 Ref range: 0.3-4.0 mCu/mL
FT4	1.34 Ref range: 0.9-1.7ng/dL
T3	62 Ref range: 80-95 ng/dL

Table 1. Clinical Features of Acromegaly.

Local tumor effects
- Pituitary enlargement
- Visual-field defects → Formal testing with no deficits
- Cranial-nerve palsy
- Headache

Somatic systems
- Acral enlargement, including thickness of soft tissue of hands and feet
- Musculoskeletal system
  - Gigantism
  - Prognathism
  - Jaw malocclusion
  - Arthralgias and arthritis
  - Carpal tunnel syndrome
  - Acroparesthesia
  - Proximal myopathy
  - Hypertrophy of frontal bones
- **Skin and gastrointestinal system**
  - Hyperhidrosis
  - Oily texture
  - Skin tags
  - Colon polyps
- **Cardiovascular system**
  - Left ventricular hypertrophy
  - Asymmetric septal hypertrophy
  - Cardiomyopathy → Dilated,Non-Ischemic
  - Hypertension → Post-tx BPs < 130/90
  - Congestive heart failure → NYHA IV
- **Pulmonary system**
  - Sleep disturbances
  - Sleep apnea (central and obstructive)
  - Narcolepsy

Visceromegaly
- Tongue
- Thyroid gland
- Salivary glands
- Liver
- Spleen
- Kidney
- Prostate

Endocrine and metabolic systems
- Reproduction
  - Menstrual abnormalities
  - Galactorrhea
  - Decreased libido, impotence, low levels of sex hormone–binding globulin
- Multiple endocrine neoplasia type 1
  - Hyperparathyroidism
  - Pancreatic islet-cell tumors
- Carbohydrate
  - Impaired glucose tolerance
  - Insulin resistance and hyperinsulinemia
  - Diabetes mellitus → A1c 5.8
- Lipid
  - Hypertriglyceridemia → TG 139
- Mineral
  - Hypercalciuria, increased levels of 25-hydroxyvitamin D_3
  - Urinary hydroxyproline
- Electrolyte
  - Low renin levels
  - Increased aldosterone levels
- Thyroid
  - Low thyroxine-binding–globulin levels
  - Goiter

ORAL GLUCOSE TOLERANCE TEST WITH GROWTH HORMONE LEVELS

Initial Inpatient OGTT – 8/28/2013

Time (min)	0	60	120
GH Ref range: 0-4.2 ng/mL	1.5	5.4	3.9

Follow-Up Outpatient OGTT – 9/11/2013

IGF-1	Time (min)	30	60	90	120
464 Ref range: 81-225 ng/mL	GH Ref range: 0-4.2 ng/mL	1.9	3.3	1.4	1.6
	Glucose	86	132	119	125

INITIAL MANAGEMENT OF ACROMEGALY

Transsphenoidal surgery – 1st line for
Intrasellar microadenomas
Noninvasive macroadenomas
Tumors causing compressive symptoms

Surgical removal provides biochemical control with IGF-1 normalization in 75-95% of patients

Contraindications to surgery:
Patient refusal, severe cardiomyopathy or respiratory disease, or lack of skilled surgeon availability

Melmed S, et al. Guidelines for acromegaly management: an update. J Clin Endocrinol Metab. 2009;94(5):1509-1517.

OUR PATIENT'S HEART – SURGICAL CANDIDATE?

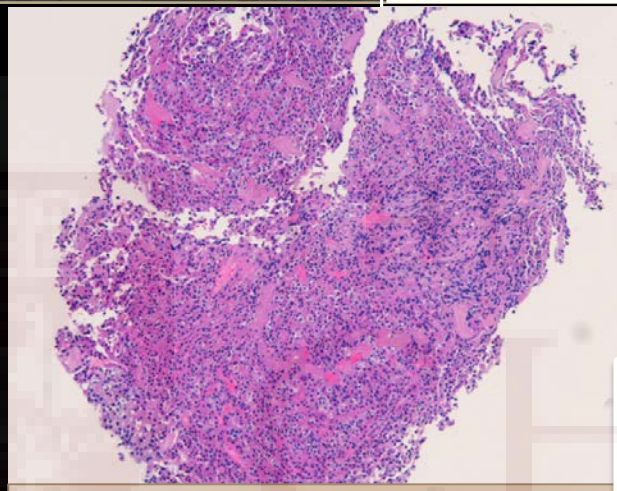
Cardiology assessment: "We discussed the patient at our transplant meeting and agreed that we should proceed with resection. He had his right heart catheterization and biopsy - his hemodynamics are good (just some dehydration). From a cardiac pre-op point of view, he would not need any other testing done."

MANAGEMENT

Patient underwent transsphenoidal resection of piutitary microadenoma on 11/4/2013.

Given his prolonged history of immunosuppression and prednisone therapy for OHT, it was recommended that he receive stress dose steroids peri-operatively.
Post-operatively, he was started on replacement corticosteroids with hydrocortisone 20 mg/10 mg daily.

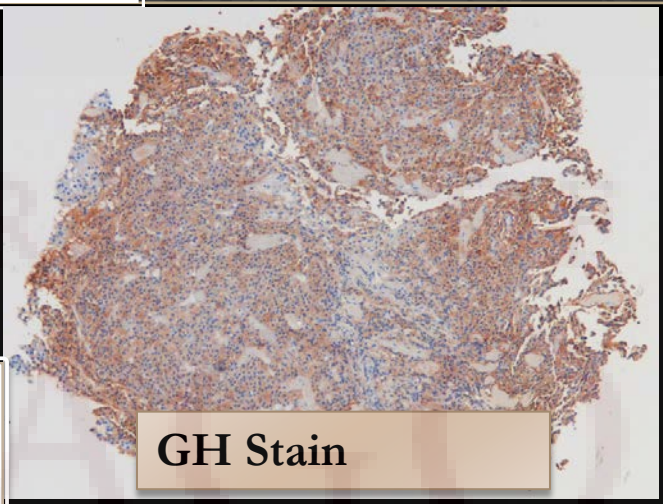
TRANSSPHENOIDAL RESECTION-PATHOLOGY



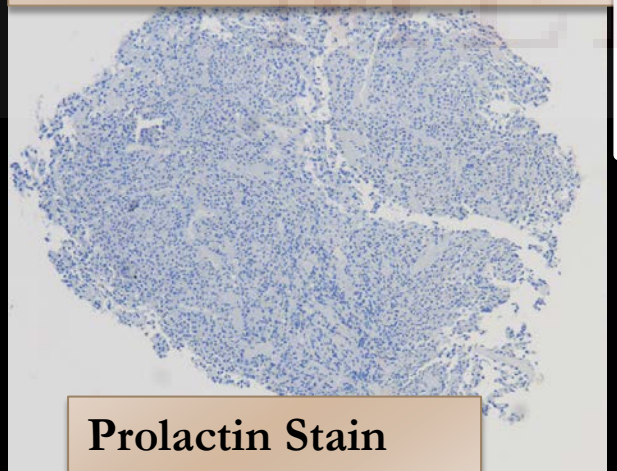
Original H&E
No expression of ACTH, TSH, Prolactin, LH, and FSH.
Patchy staining for GH

Frozen Path
2 soft-tissue adenoma fragments measuring 0.7 and 0.3 cm

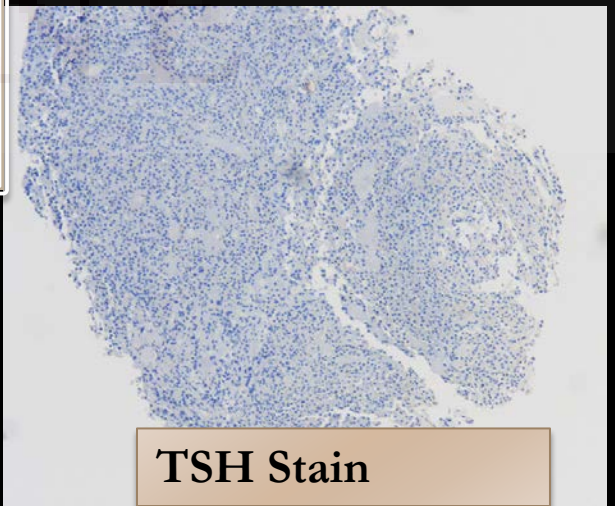
Fresh – multiple fragments from 0.1 to 0.6 cm in size



GH Stain



Prolactin Stain



TSH Stain

POST-OPERATIVE EVALUATION

	11/5/2013 05:14 (POD #1)	11/6/2013 03:41 (POD #2)
Growth Hormone Ref range: (0-4.2 ng/mL)	1.1	1.4
SMC/IGF1 Ref range: 81-225 ng/mL	474	319

	11/6/2013
TSH	1.66

24-hour UOP	1785 mL

With successful surgery, GH levels typically fall to normal within 1-2 hours (depending on level of elevation before surgery).
IGF-1 concentrations fall more slowly, from weeks to months.

Feelders RA, et al. Postoperative evaluation of patients with acromegaly: clinical significance and timing of oral glucose tolerance testing and measurement of (free) insulin-like growth factor 1, acid-labile subunit, and growth hormone binding protein levels. J Clin Endocrinol Metab. 2005;90(12):6480.

POST-OPERATIVE MANAGEMENT

Post-operatively: no visual symptoms, CSF leak, seizures, vomiting. Intermittent nausea. Headaches persist to degree that limiting his activities of daily living. Concern that anti-rejection drugs may be contributing.

Plan for post-operative IGF/GH testing in 3 months.

Above will determine need for additional therapy.

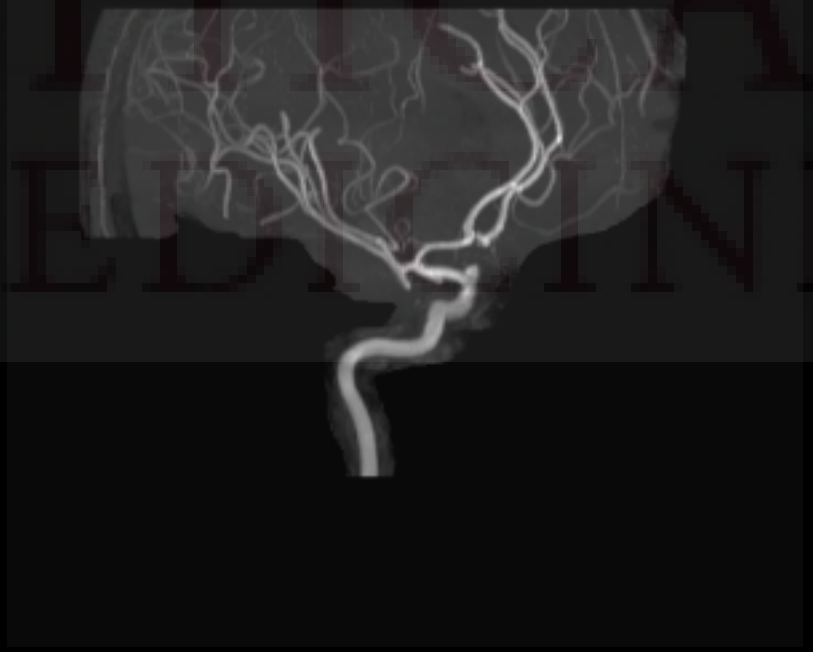
FOLLOW-UP TESTING

	12/12/2013	2/20/2014
SMC/IGF1 Ref range: 81-225 ng/mL	**359**	**275**

Due to the severity of patient's nausea, he is initially reluctant to undergo repeat OGTT to confirm persistent GH elevation.

FOLLOW-UP IMAGING

Follow-Up MRA Brain w/o: Broad-based aneurysm arising from the C6 segment of the right internal carotid artery measuring 4 x 4 x 6 mm. Limited examination of the brain.



ONGOING MANAGEMENT

Glucose Tolerance 2/20/2014	0	30	60	120	180
Growth Hormone	0.9	4.9	2.0	0.7	0.2
Glucose Ref range: (0-4.2 ng/mL)	83	106	86	61	114

Given the above findings, on 3/13 the patient is started on somatostatin 50 mcg tid with plan to transition to monthly depot somatostatin if tolerates above.

Cost and tid injections result in intermittent adherence to therapy. On 8/6, transitioned.

BIOCHEMICAL FOLLOW-UP

	12/12/2013	2/20/2014	3/13/2014	4/7/2014	5/22/2014	9/8/2014
SMC/IGF1 Ref range: 81-225 ng/mL	**359**	**275**	**298**	**273**	**266**	**181**

ASSESSING FOR CURE

TABLE 2. Acromegaly treatment outcomes

Outcome	Criteria	Management
Controlled	Nadir GH <1 μg/L Age-sex-normalized IGF-I No clinical activity	Asses GH/IGF-I axis Evaluate pituitary function Periodic MRI No treatment or no change in current treatment
Inadequately controlled	Nadir GH >1 μg/L Elevated IGF-I Clinically inactive	Assess GH/IGF-I axis Evaluate pituitary function Periodic MRI Assess cardiovascular, metabolic, and tumoral comorbidity Weigh treatment benefit or consider new treatment *vs.* low risk of elevated GH
Poor control	Nadir GH >1 μg/L Elevated IGF-I Clinically active	Assess GH/IGF-I axis Evaluate pituitary function Periodic MRI Actively treat or change treatment

Failure to control GH to a normal level is associated with a 3.5 x increased mortality as compared to patients in whom GH is controlled . Mortality in the latter is no different from controls.

Giustina A, et al. Criteria for cure of acromegaly: a consensus statement. J Clin Endorinol Metab. 2000;85(2):526-529.

CONCLUSIONS

Elevated serum IGF-1, with a Growth Hormone that fails to suppress after OGTT confirms diagnosis of acromegaly.

Surgical resection (transsphenoidal surgery) is first-line treatment for intrasellar microadenomas, noninvasive macroadenomas, and tumors causing compressive symptoms. When surgical control is not achieved, tumor anatomy is unfavorable to surgery, or patient is not a surgical candidate, medical therapies (somatostatin analogues, GHRH antagonists, and dopamine agonists), and radiation therapy can be considered.

EXTRA SLIDES

THE UNIVERSITY OF CHICAGO MEDICINE

DIAGNOSIS OF ACROMEGALY

Random GH < 0.4 μg/L and normal IGF-1 excludes acromegaly

In a normal patient, serum GH should drop to < 1 ng/mL within two hours after ingestion of a glucose load of 75 g.

In an acromegalic patient, post-glucose GH is > 2 ng/mL in > 85% of the time.

Jaffe CA, et al. Regulation of GH secretion in acromegaly: reproducibility of daily GH profiles and attenuated negative feedback by IGF-1. J Clin Endocrinol Metab 2001; 86:4364-4370.

Giustina A, et al. Criteria for cure of acromegaly: a consensus statement. J Clin Endorinol Metab. 2000;85(2):526-529.

OPTIONS BEYOND SURGERY

Comparison of treatments for acromegaly

	Surgery		Radiotherapy	Octreotide, lanreotide	Cabergoline	Pegvisomant
	Microadenoma	Macroadenoma				
Normal IGF-1	80-90 percent	40 percent	50 percent at 10 yrs	50 percent	40 percent	95 percent
Adenoma shrinkage	95 percent	70 percent	95 percent	50 percent	No data	Not expected
Advantages	Potential cure reduction	Rapid size reduction			Oral administration	
Disadvantages	Recurrence: 5-10 percent	Regrowth of adenoma	Slow	Injection		Injection
Complications						
Hypopituitarism	Rare	15 percent	50 percent at 10 yrs	None	None	None
Other	Diabetes insipidus, 5 percent	Diabetes insipidus, 10 percent	Neurological deficits	GI symptoms, gallstones	Nausea, lassitude	Elevated liver enzymes

A summary of the advantages, disadvantages, and complications of different treatments of acromegaly.

CORONAL DYNAMIC (NO POST CONTRAST CORONAL DONE)