



50-YEAR-OLD MAN WITH DECREASED LIBIDO AND HYPERCORTISOLISM

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History of Present Illness

- 50 yo man was well until he noticed reduced libido 6 – 9 months prior to presentation
- Testosterone was checked and < 200
 - started on Androgel
- Hormone therapy was discontinued 2 months later due to anxiety and rash

History of Present Illness

- Over the past 6 months
 - Fatigue
 - Left eye with discharge, ophthalmologist thought systemic illness
 - Weakness, especially in legs
 - Weight gain, 12 pounds in last two months
 - Face appears rounder and facial skin more red
 - Jacket and neck size have increased

History of Present Illness

- Old abdominal striae are pinker and new ones have appeared
- Evaluation prior to visit
 - Elevated serum cortisol
 - Normal TSH, mildly increased fT4
 - New elevated fasting blood sugar
 - Abnormal MRI pituitary
 - US of the thyroid gland with nodule, FNA recently performed

History

- Past Medical History

- Pituitary Adenoma
- Thyroid Nodule

- Past Surgical History

- Appendectomy
- Lumbar discectomy
- Vasectomy

- Social History

- Married
- Tobacco: never
- Alcohol: no
- Illicits: no

- Family History

- Mother: hyperthyroidism s/p RAI, Parkinson's disease
- Sister: hyperthyroidism s/p RAI
- Father: leukemia

History

- Allergies: NKDA until rash with Androgel
- Medications
 - Hydrochlorothiazide: 12.5 mg PO daily
 - Tramadol 50 mg PO daily



Review of Systems

- Constitutional: Positive for fatigue and unexpected weight change. Negative for fever and appetite change.
- HENT: Positive for sore throat, facial swelling, rhinorrhea and voice change (Deeper). Negative for hearing loss and trouble swallowing.
- Eyes: Positive for pain and discharge. Negative for redness.
- Respiratory: Positive for shortness of breath. Negative for cough.
- Cardiovascular: Positive for palpitations (thought anxiety-related) and leg swelling. Negative for chest pain.
- Gastrointestinal: Positive for abdominal pain and constipation (Mild). Negative for nausea, vomiting and diarrhea.
- Genitourinary: Positive for frequency and difficulty urinating.
- Musculoskeletal: Positive for joint swelling (ankles, knees).
- Skin: Positive for color change and rash.
- Neurological: Positive for weakness, numbness (Feet) and headaches (Increased but mild).
- Hematological: Negative for easy bruising/bleeding
- Psychiatric/Behavioral: Positive for disturbed wake/sleep cycle (nocturia 2-3) and dysphoric mood (Depression 6 months), and anxiety

Physical Exam

BP: **165/97** Pulse: 83 Height: 195.6 cm (6' 5") Weight: 125.283 kg (276 lb 3.2 oz)

Constitutional: He appears well-developed and well-nourished.

HENT: **Face red**, EOM and lids are normal. Pupils are equal, round, and reactive to light. **VF nl to confrontation**

Neck: Trachea normal. Normal carotid pulses present. Carotid bruit is not present. No mass and no thyromegaly present.

Cardiovascular: Normal rate, regular rhythm and normal heart sounds.

Pulmonary/Chest: Effort normal and breath sounds normal.

Abdominal: Bowel sounds are normal. There is no hepatomegaly. There is no tenderness.

Protuberant abdomen with pink striae lower abdomen and inguinal region. Hyperpigmented abdominal scar

Genitourinary: Left varicocele

Musculoskeletal: Spine without deformity or tenderness

Lymphadenopathy: He has no cervical adenopathy. He has no axillary adenopathy.

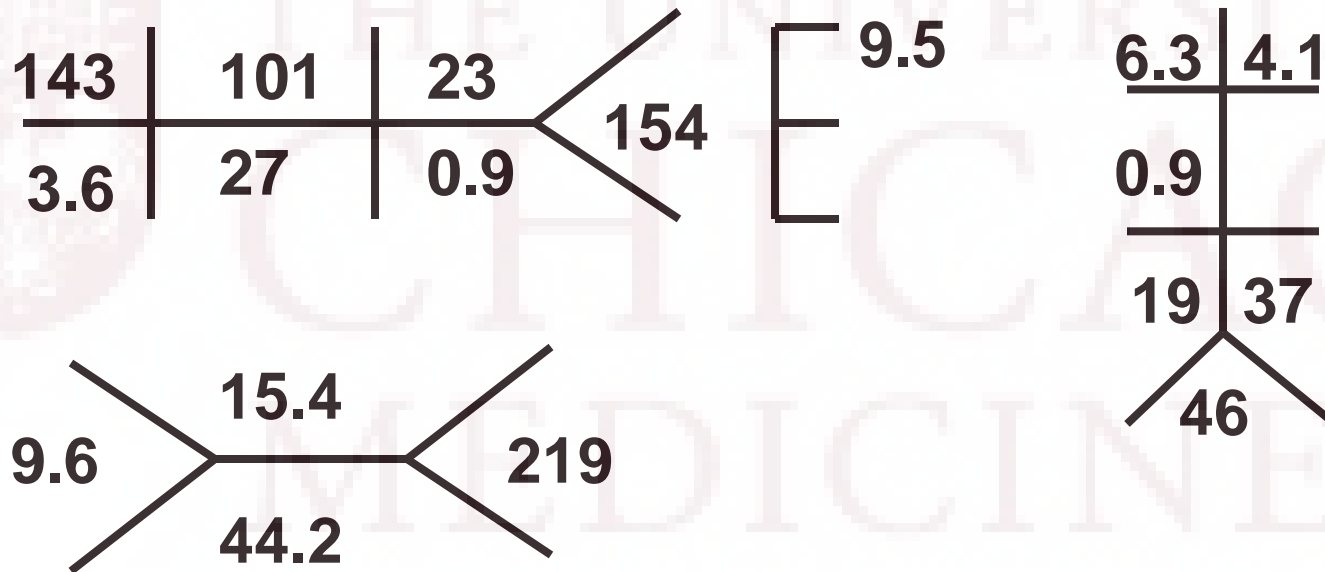
Neurological: He is alert. He displays no tremor. Bicep reflexes are 1+ on the right side and 1+ on the left side. Patellar reflexes are 1+ on the right side and 1+ on the left side.

Motor UE IV/V proximal V/V distal, LE III-IV/V proximal V/V distal

Skin: Skin is warm and dry. Rash (Fine maculopapular over lower/chest/upper abdomen) noted. He is not diaphoretic. **Red over upper chest, neck and head.** Striae as above

Psychiatric: His speech is normal and behavior is normal. Thought content normal. His mood appears anxious.

Labs and Studies



Labs and Studies

Testosterone 304 (on Androgel)

TSH 1.33. 1.12 mIU/L

fT4 2.0, 1.9 ng/dL

AntiTPO Ab 11 IU/mL (<35)

Cortisol 35.1 mcg/dL

ESR 9

CRP <0.10 mg/dL (<0.80)

ANA Screen: Negative

MRI Pituitary Report: central pituitary hypo-enhancing lesion 0.6 x 0.4 x 0.8 cm

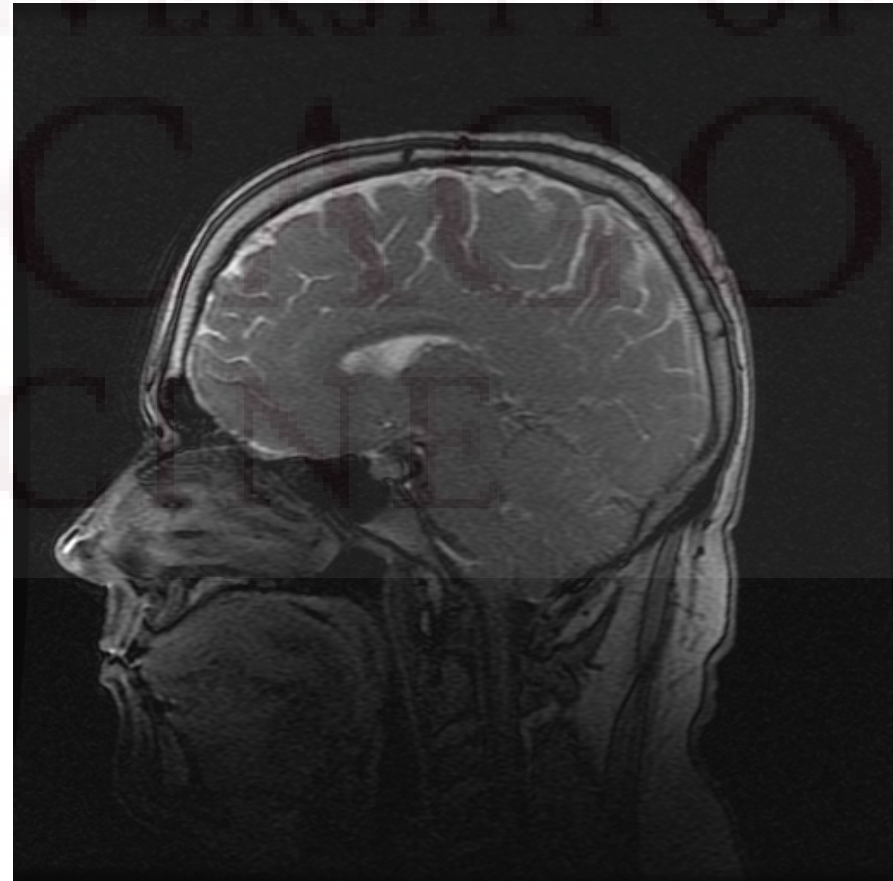
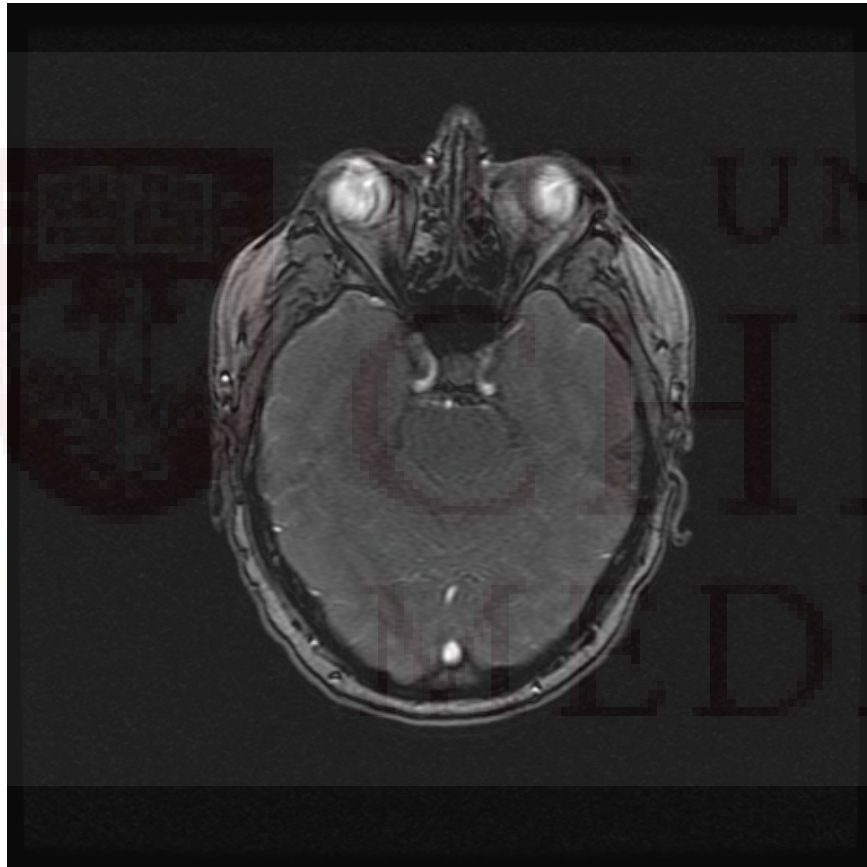
CT Abdomen Report: Normal adrenals

Thyroid US: R Lobe 5.6 x 1.6 x 2.0 cm, L Lobe 5.1 x 1.5 x 2.2 cm

Isthmus nodule hypoechoic: 1.1 x 0.6 x 1.0 cm


Cytology report: benign colloid nodule

MRI Pituitary (outside images)



The image features a dark brown vertical bar on the left side. Within this bar, there is a faint, light-colored logo of the University of Chicago Medicine, which includes a circular seal and the text "THE UNIVERSITY OF CHICAGO MEDICINE". A stylized, light-colored plant with several leaves and small, round berries is also visible, extending from the bottom left towards the center. The main area of the image is white and contains the text "INITIAL IMPRESSION?" and "NEXT STEPS?" in a dark brown, serif font.

INITIAL IMPRESSION?
NEXT STEPS?



| ACTH-dependent | ACTH-independent |
|-------------------------------|---|
| Pituitary-dependent CD | Adrenal Adenoma |
| Ectopic ACTH | Adrenal Carcinoma |
| Ectopic CRH | Primary pigmented nodular adrenal disease |
| Ectopic POMC | ACTH-independent bilateral macronodular adrenal hyperplasia |
| Exogenous ACTH administration | Exogenous glucocorticoid |
| | Bilateral disease in McCune-Albright |
| | |



Labs

LH 3.4 mIU/mL

FSH 4.6 mIU/mL

Testosterone (total) 55 ng/dL (240 – 950)

Free Testosterone (calculated) 22 pg/mL (90 – 300)

Prolactin 8.89 ng/mL (4.0 – 15.2)

IGF1 257 ng/mL (94 – 252)

Growth Hormone 0.2 ng/mL (0 – 4.2)

Cortisol 39.1 mcg/dL

TSH 0.83 mcU/mL (0.30 – 4.00)

Free T4 by dialysis (canceled by laboratory)

Triiodothyronine 89 ng/dL (80 – 195)

Potassium 3.1 mEq/L

Cortisol 37.4 mcg/dL

ACTH 160 pg/mL

24-hour urinary cortisol 2271.7 mcg/24h (4.0 – 50.0)

24-hour urinary creatinine 2.53 g/24h (0.63 – 2.50)

Midnight salivary cortisol 1.61 mcg/dL (<0.09)

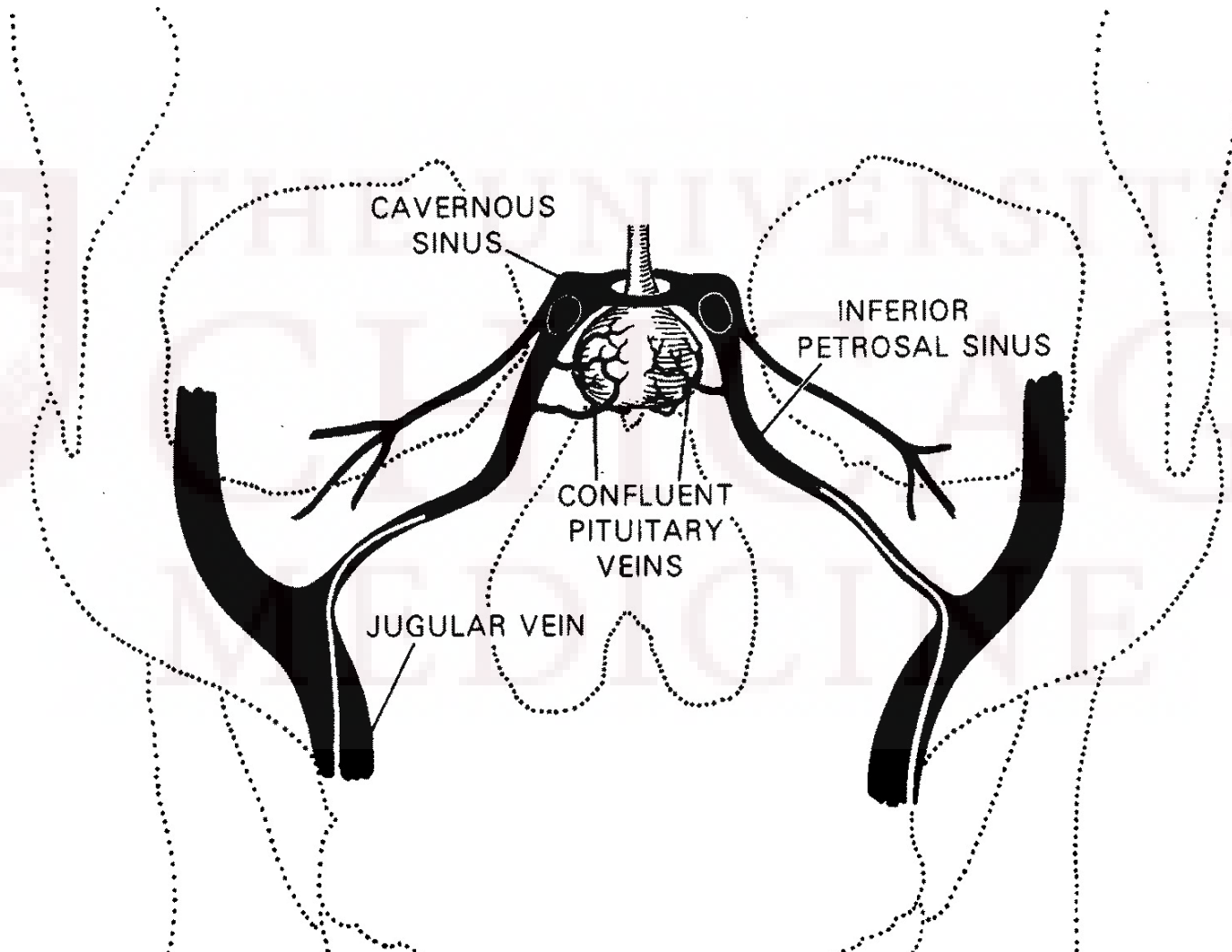
Midnight salivary cortisol 1.41 mcg/dL (<0.09)

Next Steps

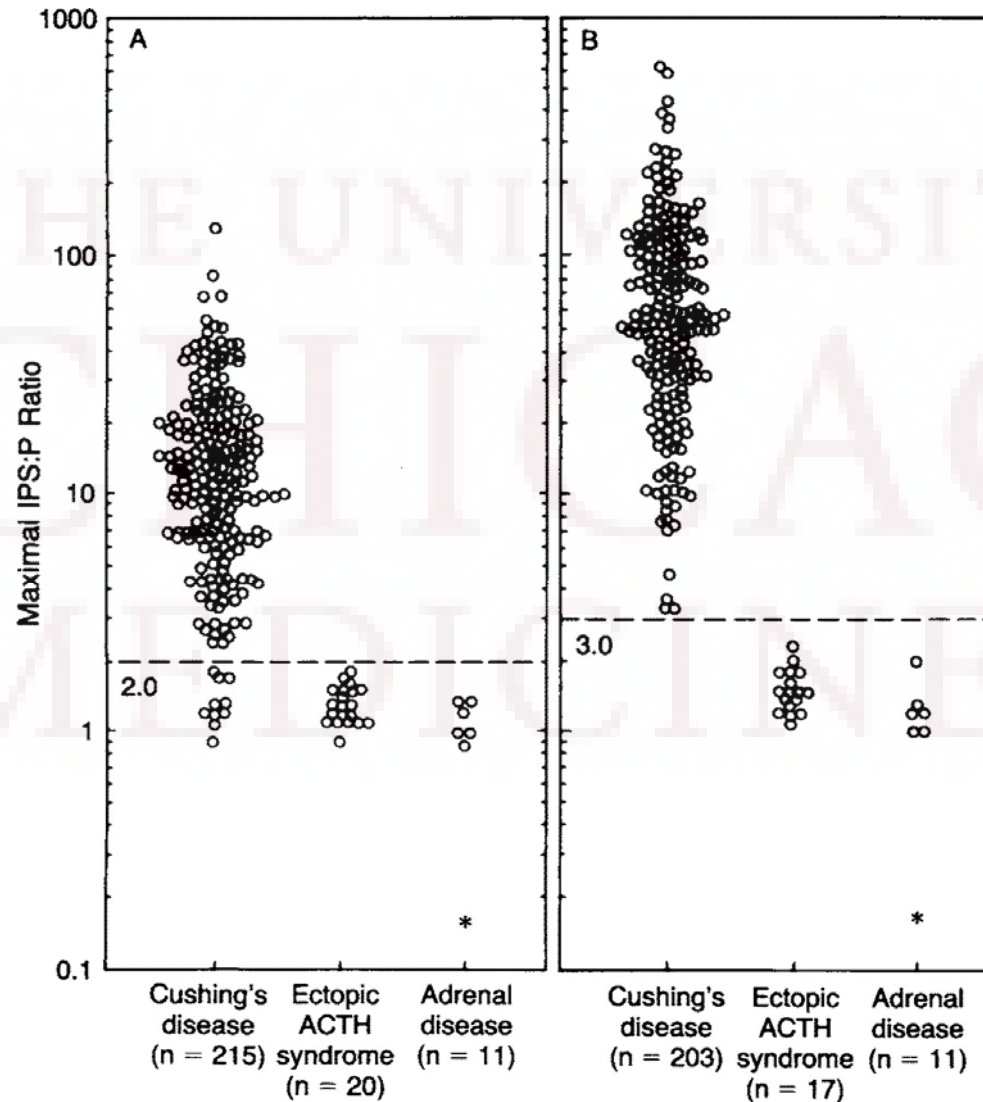
- Cushing's syndrome confirmed, etiology unclear
- Bilateral Inferior Petrosal Sinus Sampling
- CT Chest ordered
 - Rapid onset
 - Secondary Hypokalemia
 - Secondary Hypertension



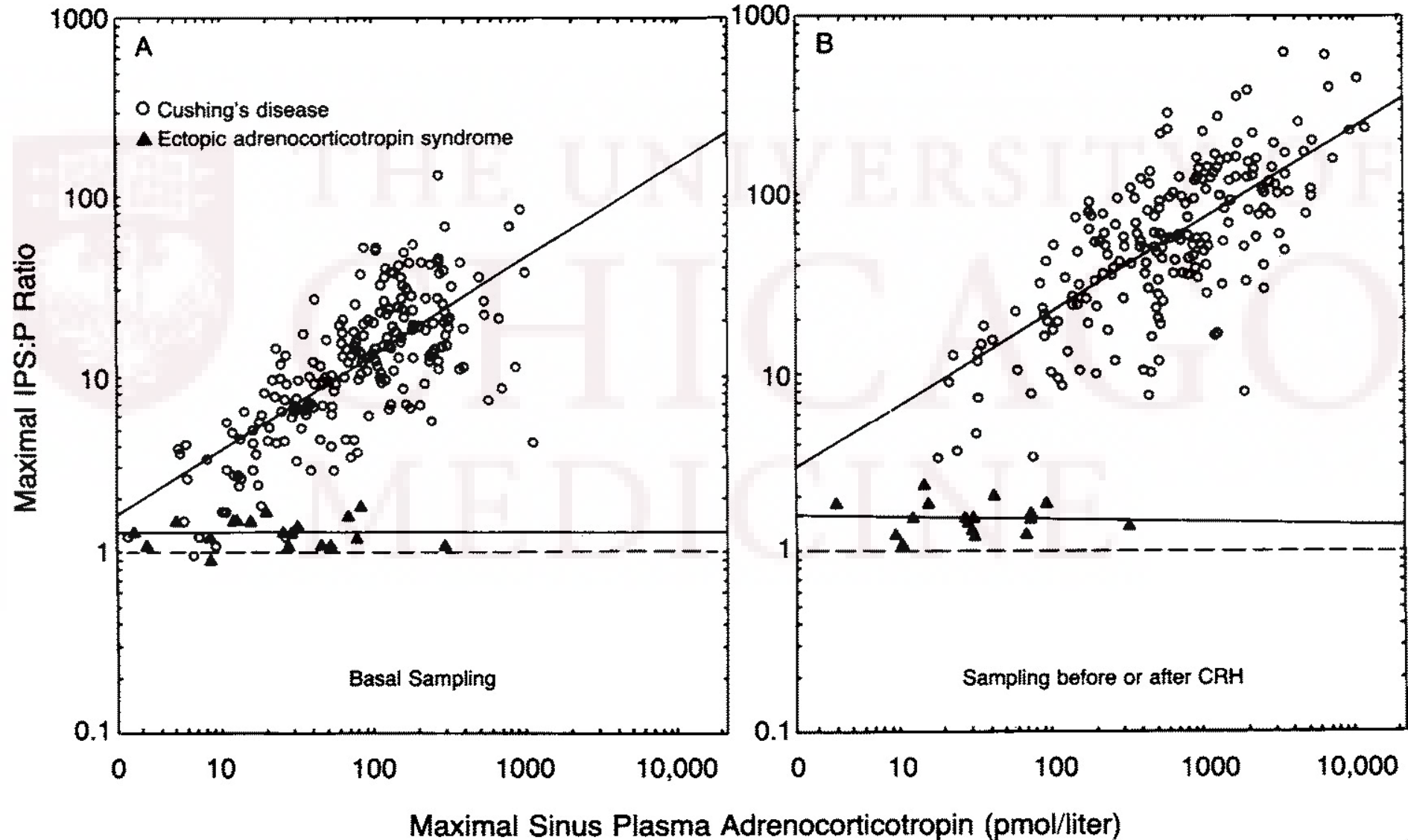
Diagnosis of Cushing's Disease



Inferior Petrosal Sinus Sampling

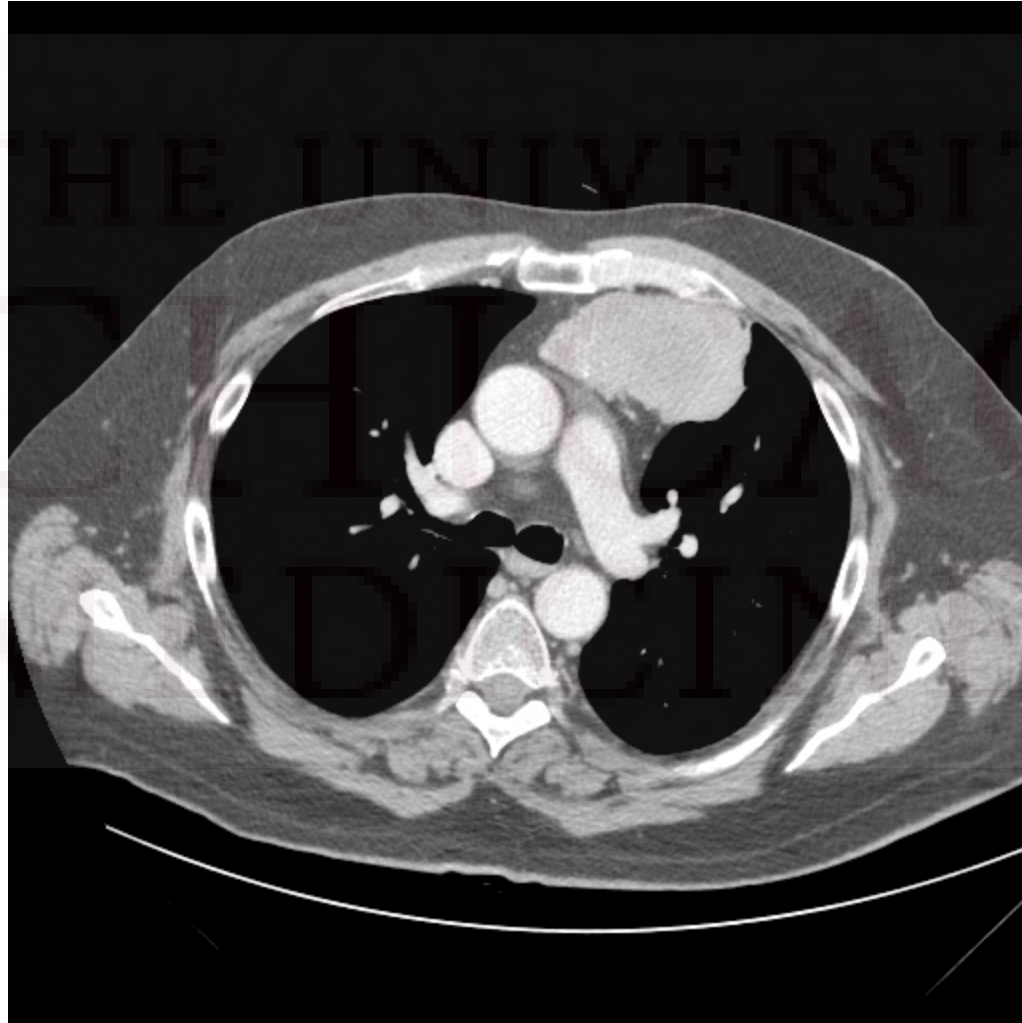


Inferior Petrosal Sinus: Plasma Ratio





CT Chest



Follow-up visit

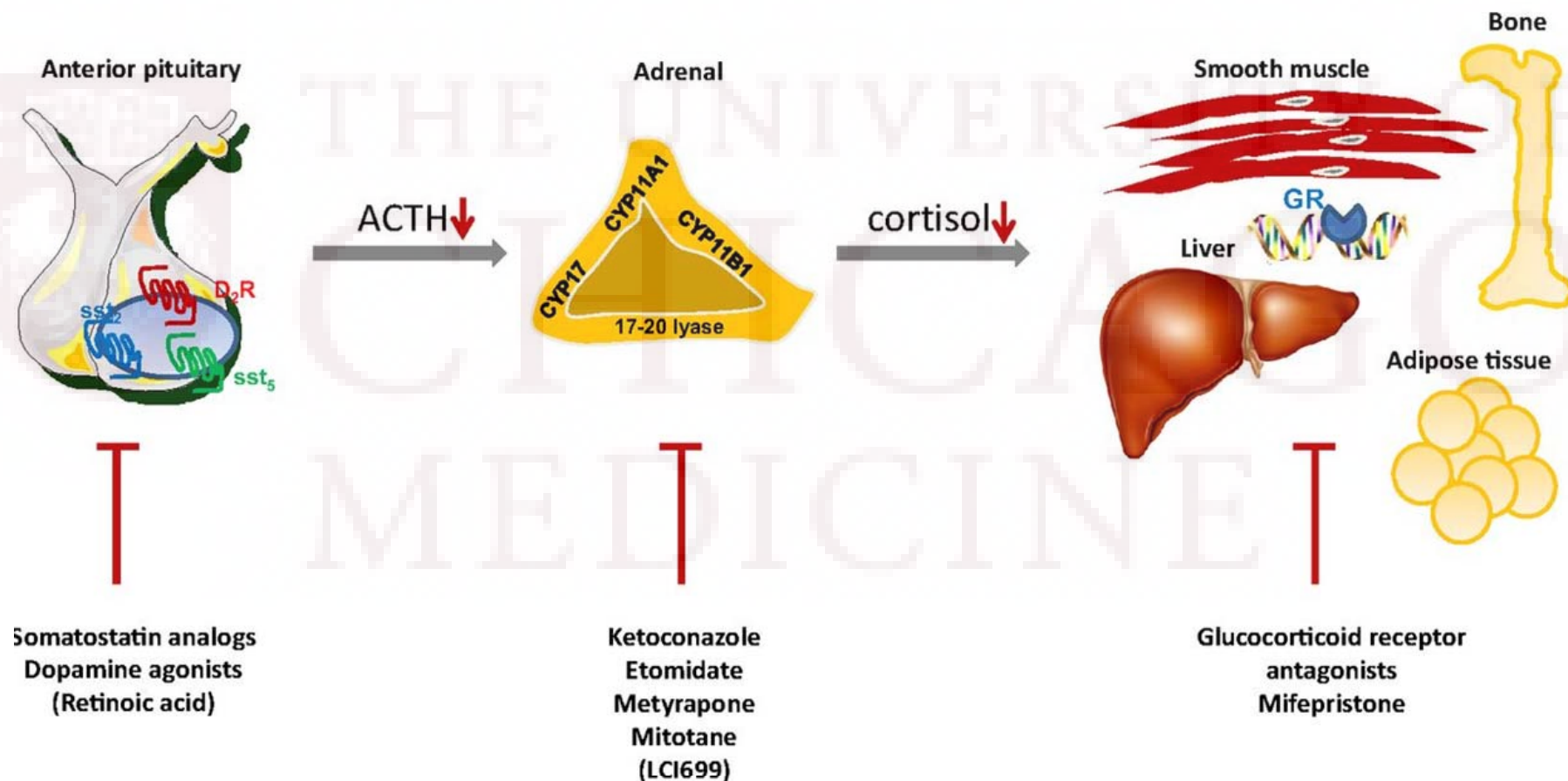
- Initial Visit: blood glucose was 154 mg/dL
- No previous history of diabetes mellitus
- Started enalapril for hypertension
- A1c elevated to 7.6%



Next Steps

- Referral to CT Surgery
- Start ketoconazole
- Return Visit
 - Diabetes Education
 - Begin Insulin Therapy
 - Add amlodipine for hypertension (169/97)
 - Discussed differential diagnosis

Medical Management





Medical Management – Inhibitors of ACTH Secretion

| Drug | Dose | Efficacy/Benefits | AE/Limitations |
|-------------|-------------------|--|---|
| Octreotide | | 50% response in ectopic ACTH, short-term responses | Poorly effective for Cushing's disease |
| Pasireotide | 600-900 mg SQ BID | Phase 3 results: Median UFC change from baseline was -47.9%; UFC normalization in 20.4%; Early identification of nonresponders | similar to other somatostatin analogs, with the addition of hyperglycemia |
| Cabergoline | 1.5-7 mg/week PO | Initial remission in up to 50%; variable responses | Nausea, dizziness, hypotension, possible cardiac valvulopathy at high doses; escape from effect on cortisol |

Medical Management - Inhibitors of adrenal steroidogenesis

| Drug | [7-26-2013] The U.S. Food and Drug Administration (FDA) is taking several actions related to Nizoral (ketoconazole) oral tablets, including limiting the drug's use, warning that it can cause severe liver injuries and adrenal gland problems and advising that it can lead to harmful drug interactions with other medications. | | |
|--------------|---|--|---|
| Ketoconazole | | | |
| Metyrapone | 500-6000 mg/day PO | Up to 80% of patients with controlled cortisol | Escape from effect on cortisol, increased ACTH, hirsutism, hypokalemia, hypocortisolism |
| Mitotane | Up to 6000 mg/day PO | Up to 90% short-term remission in ectopic ACTH; up to 70% remission in Cushing's disease | Slow onset of action; poor tolerability due to neurologic, GI, and hepatic effects |
| Etomidate | 0.03-0.3 mg/kg/hr IV | Rapid onset; useful for acute control of severe hypercortisolism | Sedation, parenteral |



Cholesterol

Metyrapone, Mitotane

Pregnenolone $\xrightarrow{3\beta\text{HSD1 \& 2}}$ Progesterone $\xrightarrow[\text{POR}]{\text{P450c21}}$ 11-Deoxycorticosterone $\xrightarrow{\text{Fdx/FdR}}$ Aldosterone

Etomidate

**Metyrapone, Mitotane,
Ketoconazole**

**Etomidate, Ketoconazole,
Metyrapone, Mitotane**

17OH-Pregnenolone $\xrightarrow{3\beta\text{HSD}}$ 17OH-Progesterone $\xrightarrow[\text{POR}]{\text{P450c21}}$ 11-Deoxycortisol $\xrightarrow{\text{11}\beta\text{HSD1, H6PDH}}$ Cortisol

$\xrightarrow[\text{P450c17 POR+b}_5]{}$

DHEA

Ketoconazole

$\xleftrightarrow[17\beta\text{HSD2}]{17\beta\text{HSD1}}$

Androstenediol

$\xrightarrow{3\beta\text{HSD}}$ **Androstenedione** $\xleftrightarrow[17\beta\text{HSD2}]{17\beta\text{HSD3 AKR1C3}}$

$\xrightarrow[\text{POR}]{\text{P450aro}}$

Estrone

$\xleftrightarrow[17\beta\text{HSD2}]{17\beta\text{HSD1}}$

Cortisone

$\xleftrightarrow[11\beta\text{HSD2}]{11\beta\text{HSD1, H6PDH}}$

$\xrightarrow{3\beta\text{HSD}}$

Testosterone

$\xrightarrow[\text{POR}]{\text{P450aro}}$

Estradiol

$\xrightarrow{5\alpha\text{-Reductase1 \& 2}}$

Dihydrotestosterone

$\xleftrightarrow[17\beta\text{HSD6 (3}\alpha\text{HSD activities)}]{\text{AKR1C1-4}}$ **5 α -Androstane-3 α ,17 β -diol**

$\xleftrightarrow[17\beta\text{HSD3}]{17\beta\text{HSD2}}$ **Androsterone**

$\xleftrightarrow[17\beta\text{HSD3}]{17\beta\text{HSD2}}$

5 α -Androstane-3,20-dione

$\xleftarrow{17\beta\text{HSD6 (3}\alpha\text{HSD activities)}}$



Medical Management – Inhibitors of ACTH Secretion

| Drug | Dose | Efficacy/Benefits | AE/Limitations |
|--------------|--------------------|--|---|
| Mifepristone | 300-1200 mg/day PO | Clinical responses in up to 87% of patients; improved glucose metabolism, insulin sensitivity, weight loss | Hypokalemia; vaginal bleeding; inability to use cortisol levels for monitoring; nausea/ fatigue common; |

Only medication FDA-approved for use in Cushing's syndrome (with associated DM)

Trans-sternal Thymectomy

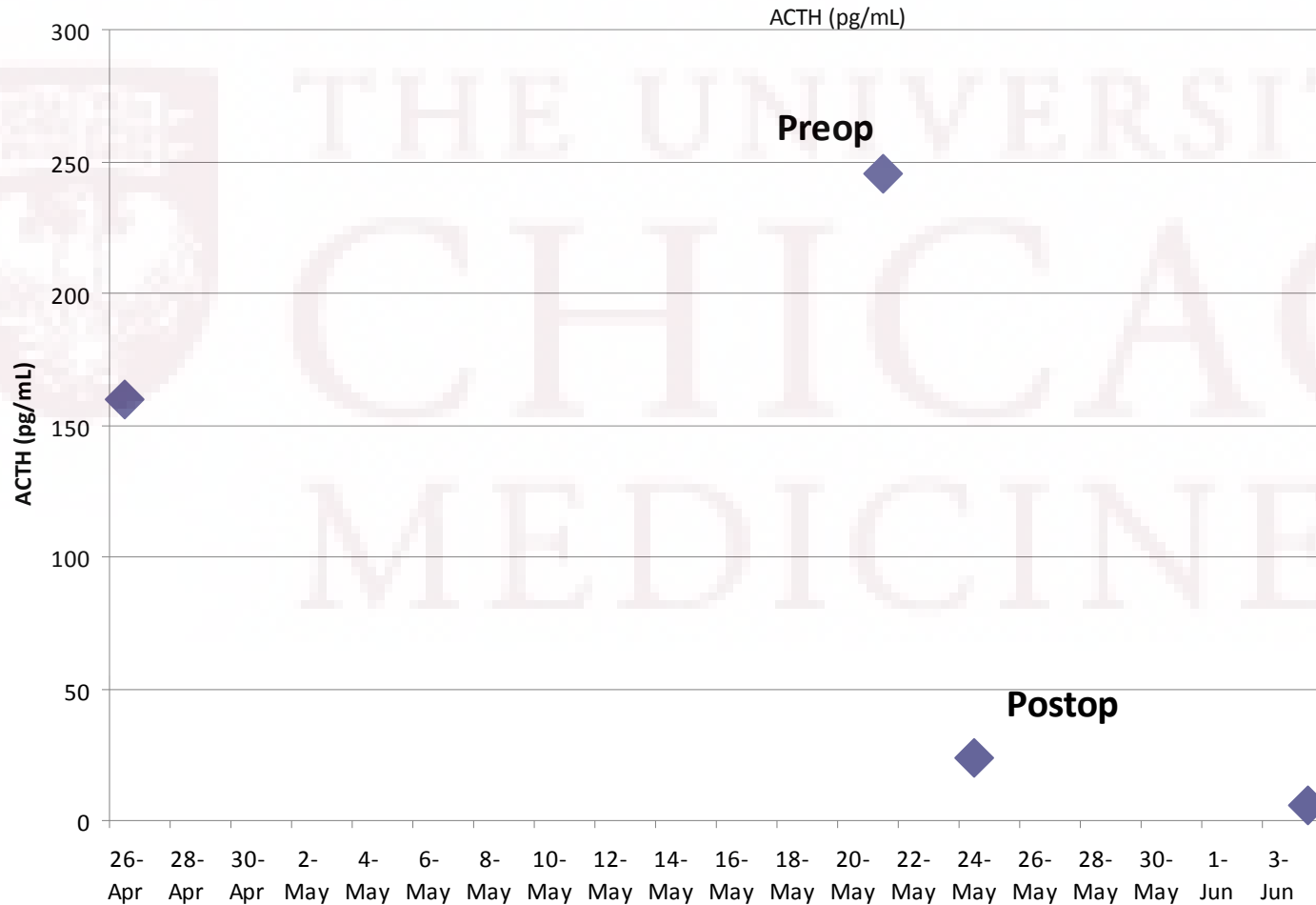
- Large mass in the left thymic lobe which was attached to the upper lobe of the lung
- A small wedge resection of the lung was performed to separate it from the thymus
- Plastic surgery followed sternectomy given concern for possible poor bone healing with hypercortisolism → closed sternum with multiple titanium plates



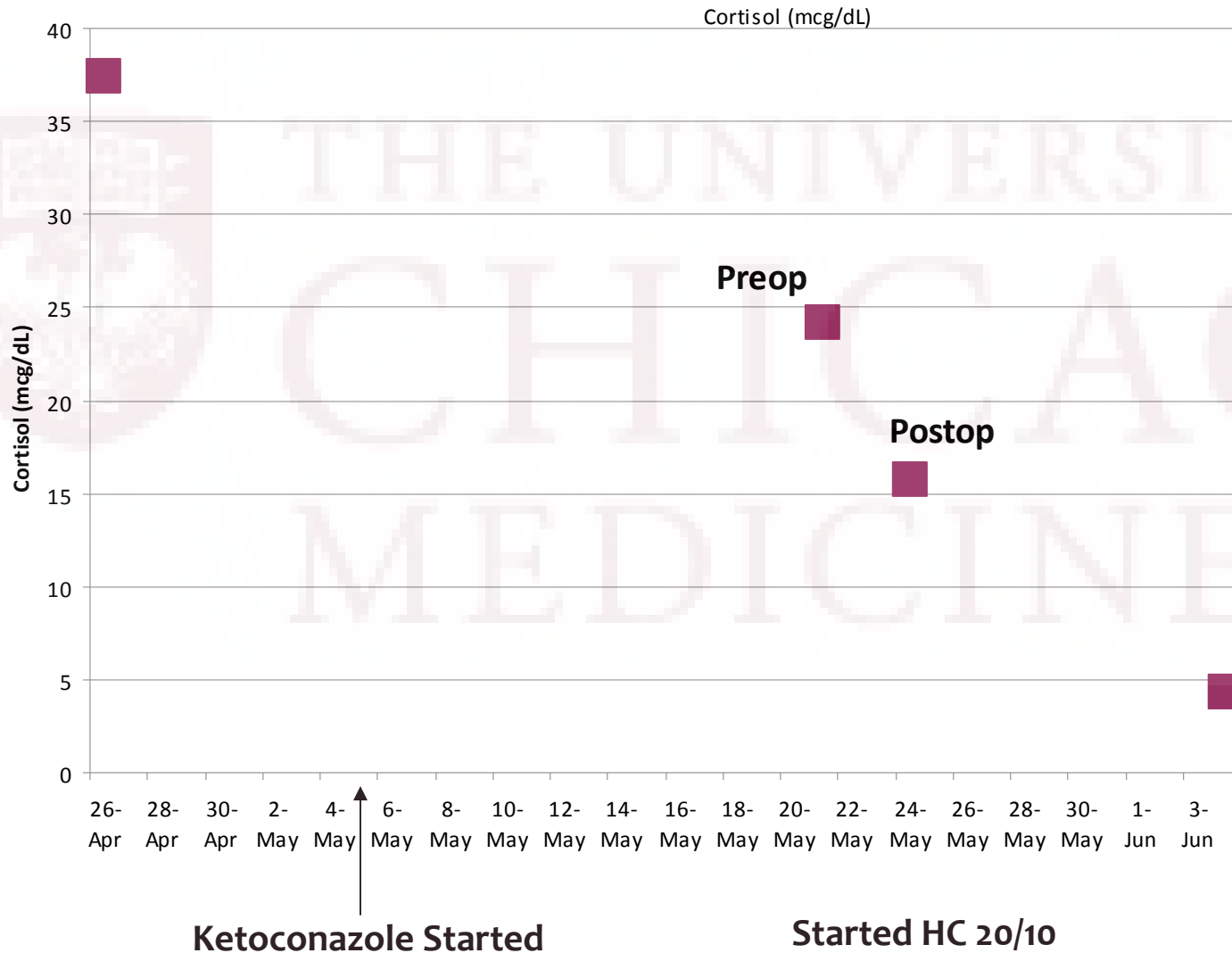
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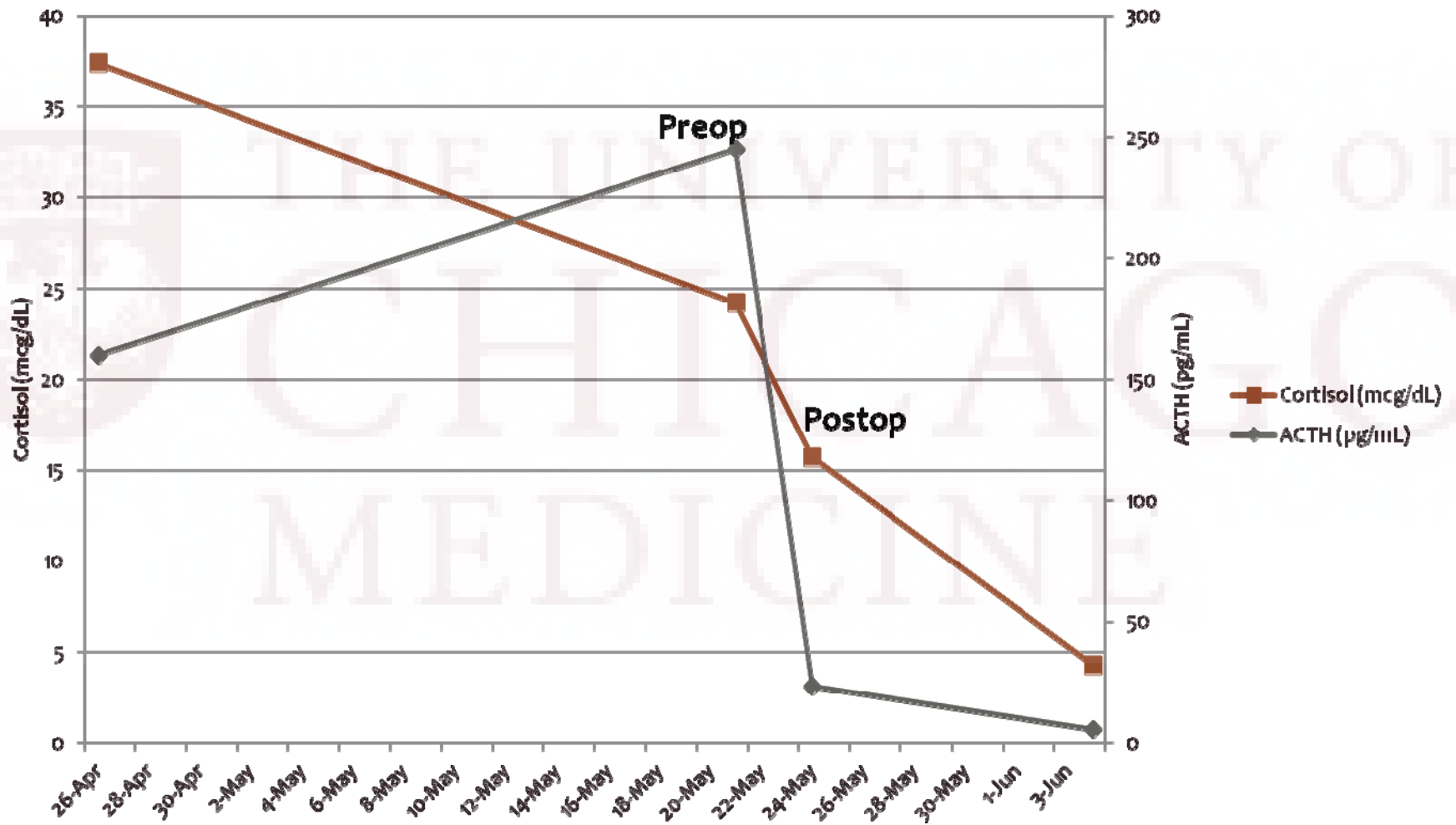
ACTH Levels



Cortisol Levels



ACTH and Cortisol Levels

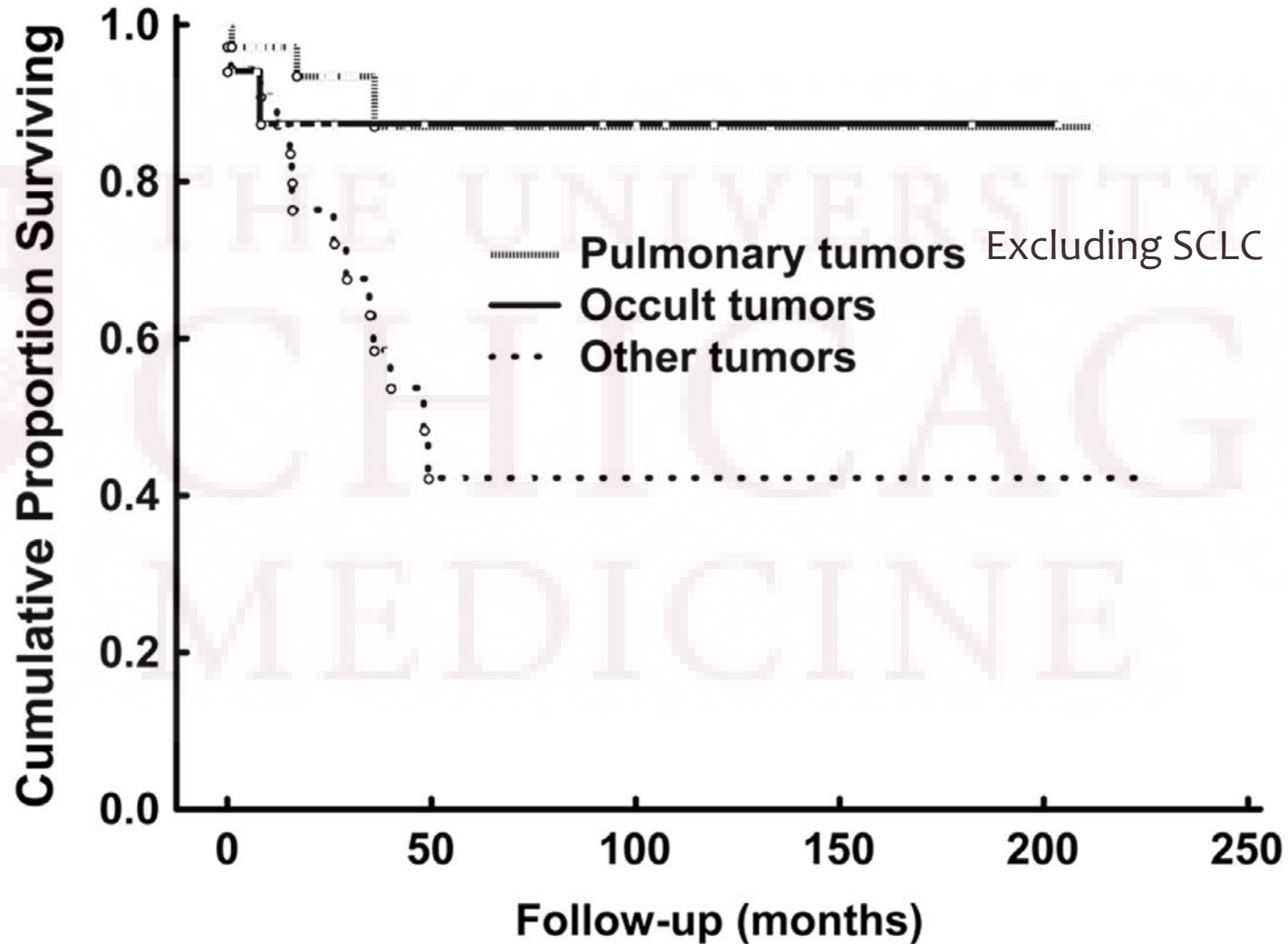


Post-operative course

- Started hydrocortisone 20/10
- Insulin requirements declined from insulin glargine 26 units daily, insulin aspart 14 units with meals plus correction → insulin glargine 10 units daily plus correction → correction only (plus metformin, BG 100-150 mg/dL)
- Hypertensive regimen adjusted from amlodipine 10 mg daily plus enalapril 10 mg daily plus spironolactone 25 mg BID → amlodipine only (BP 100-120/60-70 mmHg)



Survival Curves



20-Year History of Ectopic Cushing's at NIH

- 90 patients aged 8-72 years with ectopic ACTH from 1983 – 2004
- 86 to 94% of patients did not respond to CRH or dexamethasone suppression
- 66 of 67 had negative IPSS
- To control hypercortisolism
 - 62 patients received medical treatment
 - 33 had bilateral adrenalectomy
- Imaging localized tumors in 67 of 90 patients
- Surgery confirmed an ACTH-secreting tumor in 59 of 66 patients and cured 65%
- Nonthymic carcinoids took longest to localize.
- Deaths included
 - three of 35 with pulmonary carcinoid
 - two of five with thymic carcinoid
 - four of six with gastrinoma
 - two of 13 with neuroendocrine tumor
 - two of two with medullary thyroid cancer
 - one of five with pheochromocytoma
 - three of three with small-cell lung cancer
 - two of 17 with occult tumor



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**BACK TO OUR
PATIENT**

Referred to Oncology

- Staging with PET-CT and octreotide scan
- Plan to initiate chemotherapy with cisplatin and etoposide as well as radiation therapy
- Tumor marker will be ACTH

Plasma CRH sent post-operatively = 4.3 pg/mL (ref range up to 10.0 pg/mL)

HPA Axis/Secondary Diagnoses

Repeat ACTH <5.0 pg/mL, cortisol 3.1 mcg/dL

- Hydrocortisone reduced to 20/5 → 15/5 → 10/5 (maintenance for now)

On metformin only for diabetes

Blood pressure well-controlled on amlodipine only, last recorded 104/66 mm Hg

References

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