



Cushing Syndrome MTP

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Day 1 – 27th August – 4:15 – 5:15 PM

DISCLOSURE*

Relevant Financial Relationship(s):

None

Off Label Usage:

None

*A provider must disclose the above information to learners prior to beginning of the educational activity (ACCME)

Cushing Syndrome

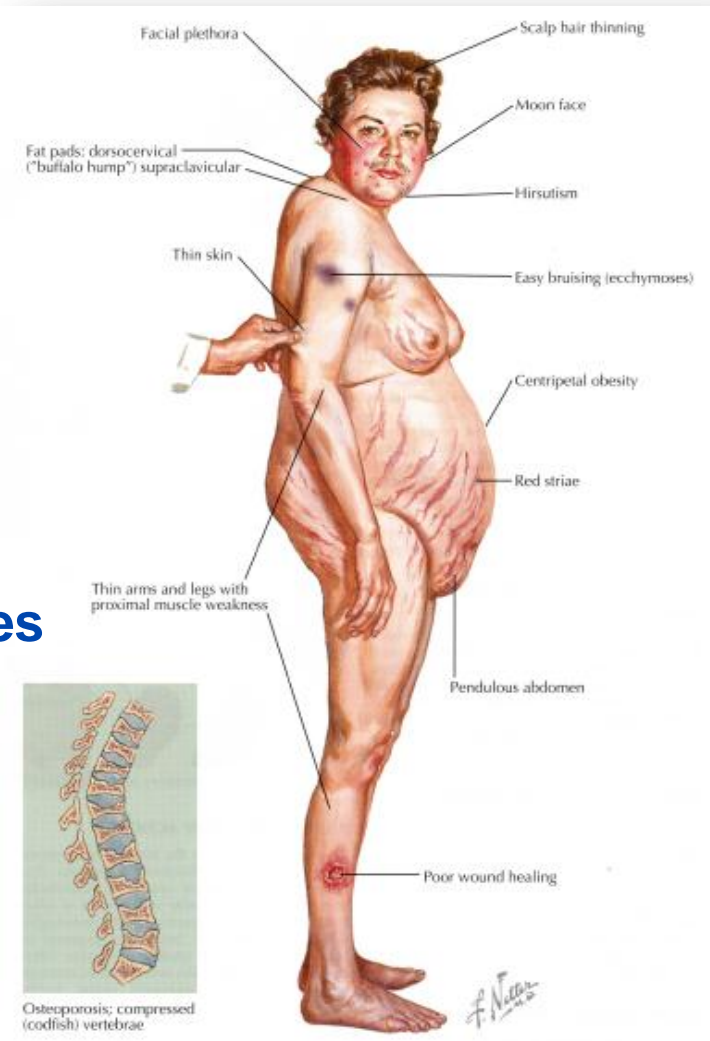
- **Clinical Overview—
emphasis on clinical and
biochemical phenotypes**
- **4 Cases:** **But, first . . .**
 - ✓ **CPC format**

Cushing Syndrome – Why it is so Hard

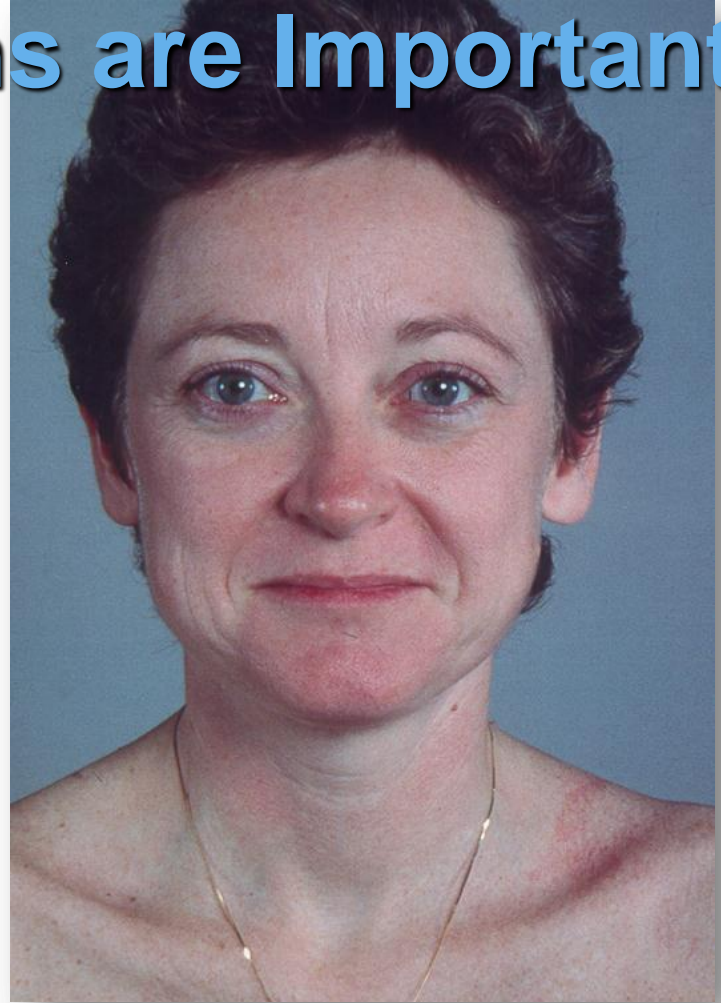
- Most difficult question:
Does the patient have CS?
- Second most difficult question: **In ACTH-dependent disease, is it pituitary or ectopic?**
- Third most difficult question:
If it is ectopic, where is it?
- Fourth, unlike other endocrine disorders, **there is no single test—you need to build a wall of evidence**

- Weight gain with central obesity & **thin extremities**
- Facial rounding and **plethora** – “moon facies”
- Dorsocervical fat pad “buffalo hump” & **supraclavicular fat pads**
- Easy bruising, fine “cigarette paper thin” skin, poor wound healing, **wide (>1-cm) purple-red striae**, hirsutism, acne, fungal skin infections
- **Proximal muscle weakness & thin extremities**
- Emotional and cognitive changes
- Hypertension, diabetes mellitus, osteoporosis
- Gonadal dysfunction

Young WF Jr: The Netter Collection of Medical Illustrations: Endocrine System, Volume 2, 2nd Edition, Page 76, © 2011 by Saunders.



Serial Photographs are Important



Serial Photographs are Important



Clinical Suspicion of Cushing Syndrome (CS)



Case Detection Tests:

- 24-hr UFC
- Midnight salivary cortisol
- 1-mg overnight DST
- Diurnal serum cortisols
- Old photographs

Dependent on your degree of clinical suspicion, use 1 or all 5

Clinical Suspicion of Cushing Syndrome (CS)



Case Detection Tests:

- 24-hr UFC
- Midnight salivary cortisol
- 1-mg overnight DST
- Diurnal serum cortisols
- Old photographs

TIP: In the patient with obvious and severe CS, don't waste time with 1-mg DST or salivary cortisol—get 24-hr UFC, a.m. serum cortisol and serum ACTH

Case Detection Testing for Clinical CS

- **AM/PM cortisol (8 AM / 4 PM):**
 - Normal = 18 mcg/dL / 9 mcg/dL
 - Suspect CS if 18 mcg/dL / 18 mcg/dL
- **24-hr UFC (ULN <45 mcg)**
 - > 200 mcg – must be CS
 - < 45 mcg – unlikely CS
- **MN Salivary cortisol (ULN < 100 ng/dL)**
 - > 100 ng/dL – suspicious
 - > 200 ng/dL – likely CS
- **1 mg DST (N <1.8 mcg/dL)**
 - ≤ 1.8 mcg/dL – usually normal
 - > 1.8 mcg/dL – might be abnormal
- **Old photographs**

Oral estrogen
Night shift/jet lag
Depression

High urine volume
(>4 L)

If >1000 ng/dL -
contamination

Pit CS can suppress
<1.8; a lot of false
+’s between 1.8 – 5

Non-CS weight gain

Example of “Don’t Waste Time”

LAB AG Continuous	Reference Range	MCR 19Aug15 11:00	MCR 19Aug15 09:01	MCR 19Aug15 09:00
<input type="checkbox"/> Prolactin(S)	4.0 - 15.2 ng/mL		21.8 * @0B	
<input type="checkbox"/> Cortisol.	a.m. : 7-25; p.m. : 2-14...			
<input type="checkbox"/> AM Cortisol	7-25 mcg/dL		28 * ←	
ENDOCRINE 3 AG				
<input type="checkbox"/> Insulin-Like Growth Factor ...	83 - 344 ng/mL		203	
<input type="checkbox"/> Corticotropin(P)	10-60 (a.m. collection) ...			227 * ←
<input type="checkbox"/> Calcitonin(S)	Basal: <16; Peak Calcium...			
<input type="checkbox"/> Chromogranin A, S	<93 ng/mL			
Microbiology				
Metals 63 AG				
URINE CHEMISTRIES AG				
<input type="checkbox"/> Creatinine Clearance AG				
<input type="checkbox"/> URINE CHEMISTRY 2 AG				
<input type="checkbox"/> Creatinine(U).	SeeComment ng/spec	1777 @0A		
<input type="checkbox"/> Creatinine Conc....	mg/dL	76		
<input type="checkbox"/> Collectn Duration (w/CREAU)	h	24		
<input type="checkbox"/> Urine Volume (w/CTU)	mL	2338		
<input type="checkbox"/> URINE ENDOCRINE 2 AG				
<input type="checkbox"/> Cortisol, Free(U)	3.5-45 mcg/24 h	2104 *	←	
<input type="checkbox"/> Collectn Duration (w/CORTU)	h	24		
<input type="checkbox"/> Urine Volume (w/CORTU)	mL	2338		

Example of "Don't Waste Time"

18-Aug-2015 16:24:00

Exam: CT CHEST w + 3D Depend WS

NORM

Indications: Cushing's Syndrome; Hypertension (HTN) NOS

ORIGINAL REPORT - 18-Aug-2015 17:17:00

EXAM: CT scan of the Chest with IV contrast including 3D maximum intensity projections/volume renderings on a non-independent workstation

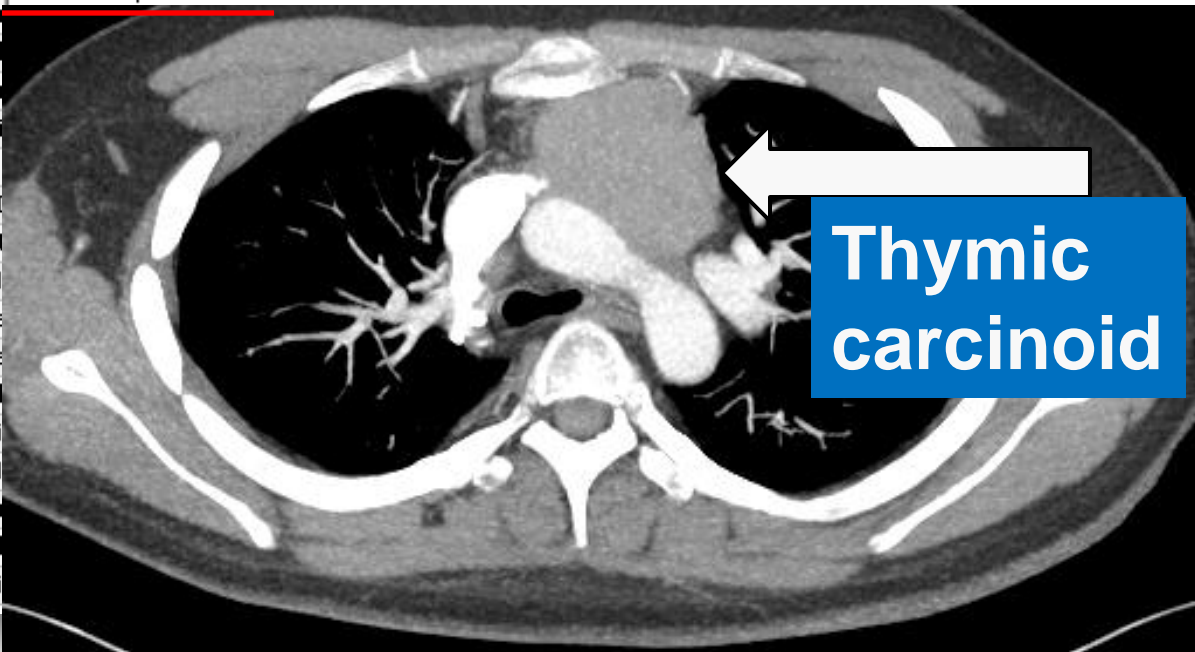
COMPARISON: No comparisons available.

IMPRESSION:

1. 5.8 cm mass in the anterior mediastinum with possible involvement of the aorta and left brachiocephalic vein.

MCR
19Aug15
09:00

227 *



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Cushing CPC

Format:

- 4 Unknown cases



- Brief History of Present Illness
- Diagnostic & Treatment Menus
- ≈15 minutes per case – including Q & A after each case

26-Year-Old Woman

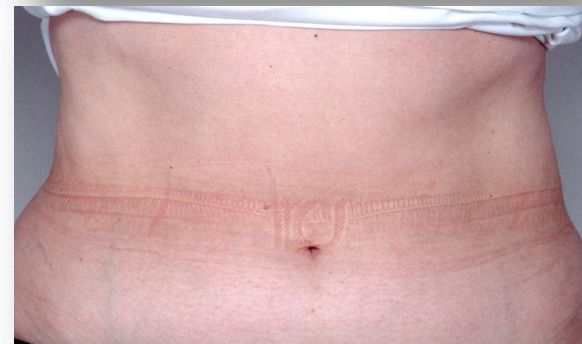
History of Present Illness:

- 4-year history of:
 - ✓ facial and neck plethora
 - ✓ acne, easy bruising
 - ✓ redistribution of body fat (14# wt gain)
 - ✓ fatigue, weakness, insomnia (aerobics instructor)
 - ✓ new hypertension (lisinopril)
 - ✓ amenorrhea x 4 yrs -- pregnancy with clomiphene 1 yr ago -- currently Rx with OCP

26-Year-Old Woman

Physical Exam:

- Height = 158 cm, weight 70.1 kg, BMI = 27.9 kg/m²
- BP 120/85 mm Hg
- Normal muscle strength, no striae



Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

Serum Cortisols

- 8 a.m. -- 30 $\mu\text{g}/\text{dL}$ (828 nmol/L)
(N < 25 $\mu\text{g}/\text{dL}$, < 690 nmol/L)
- 4 p.m. -- 32 $\mu\text{g}/\text{dL}$ (883 nmol/L)
(N < 14 $\mu\text{g}/\text{dL}$, < 386 nmol/L)

***** Remember -- Taking OCP *****

Cushing Syndrome

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24-Hour Urinary Free Cortisol

- 88 μg (N < 45 $\mu\text{g}/24\text{-hr}$)
243 nmol/d (N < 124 nmol/d)

False + with:

ETOHism

Depression

Anorexia nervosa

Severe illness (eg, ICU)

Carbamazepine (HPLC assays)

High urine volume (eg, > 4L)

> 24-hr collection

Cushing Syndrome

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Serial Photographs

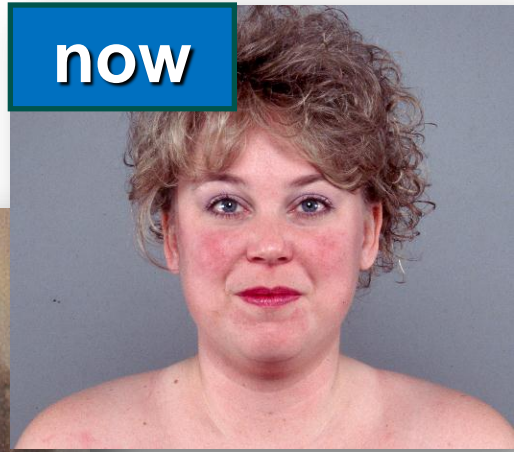
5 yrs
ago



3 yrs ago



now



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2-Day Low-Dose DST

- 24-hr UFC = 3.2 μg (8.8 nmol/d)
(N < 10 μg , < 28 nmol/d)

Sensitivity = “96%”

Specificity = 70%

Patients with mild pituitary-dependent CS can suppress with low-dose DST

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
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Monthly 24-hr UFC

2 months later (OCP D/C):

- Serum cortisol:
 - ✓ 8 a.m. -- 20 $\mu\text{g/dL}$ (552 nmol/L)
(N < 25 $\mu\text{g/dL}$, < 690 nmol/L)
 - ✓ 4 p.m. -- 22 $\mu\text{g/dL}$ (607 nmol/L)
(N < 14 $\mu\text{g/dL}$, < 386 nmol/L)
- Midnight salivary cortisol =
220 ng/dL (N < 100 ng/dL)
6.1 nmol/L (N < 2.8 nmol/L)
- 24-hr UFC = 90 μg (248 nmol/d)
(N < 45 μg , < 124 nmol/d)

Clinical Suspicion of Cushing's Syndrome (CS)

26-Year-Old Woman

Physical Exam:

- Ht = 158 cm, wt = 70.1 kg, BMI = 27.9 kg/m²
- BP 120/85 mm Hg
- Normal muscle strength,



Case Detection Tests:

- 24-hr UFC
- Midnight salivary cortisol
- 1-mg overnight DST
- Diurnal serum cortisols
- Old photographs



NO RUSH!

Borderline or Normal
CS unlikely

Re-evaluate if strong
clinical suspicion
Consider monthly 24-hr
UFC—**these pts will
NOT die from CS!!!**

UFC 200 - 1000 mcg
+ clear CS on exam

Pursue subtype testing
promptly

UFC >1000 mcg

Pursue subtype
testing ASAP!!!
**These pts do die
from CS!!**

Clinical Suspicion of Cushing's Syndrome (CS)

26-Year-Old Woman

Physical Exam:

- Ht = 158 cm, wt = 70.1 kg, BMI = 27.9 kg/m²
- BP 120/85 mm Hg
- Normal muscle strength,



Case Detection Tests:

- 24-hr UFC
- Midnight salivary cortisol
- 1-mg overnight DST
- Diurnal serum cortisol
- Old photographs



NO PUSH!

TIP: The “biochemical phenotype” guides the urgency to resolve the diagnosis and treat for a cure

Clinical suspicion

Consider monthly 24-hr UFC—these pts will **NOT die from CS!!!**

promptly

testing ASAP!!!

These pts do die from CS!!

Cushing Syndrome

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Dex-CRH Test

- Not Done

Cushing Syndrome

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Midnight Salivary Cortisol x 2

- 120 ng/dL (N < 100 ng/dL)
3.3 nmol/L (N < 2.8 nmol/L)
- 132 ng/dL (N < 100 ng/dL)
3.6 nmol/L (N < 2.8 nmol/L)

Sensitivity = 92%

Specificity = 93%

Raff et al., 1998

Castro et al. 1999

Findling and Raff, 2006

Kidambi et al., 2006

Cushing Syndrome

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1-mg Overnight DST

- 8 a.m. serum cortisol =
1.7 $\mu\text{g/dL}$ (46.9 nmol/L)
(N < 1.8 $\mu\text{g/dL}$, < 50 nmol/L)

18% of patients with pituitary-dependent CS suppress to < 5 $\mu\text{g/dL}$ (138 nmol/L) with overnight 1-mg DST—thus, to reach a sensitivity of >95% a cut-off of 1.8 $\mu\text{g/dL}$ (138 nmol/L) should be used; specificity = 80%

Cushing Syndrome

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Serum ACTH

- 45 pg/mL (N, 10 – 60)

Confirmed Cushing Syndrome (CS)



Serum ACTH

Undetectable

Mid-normal to increased

Adrenal CT

Pituitary MRI

Unilateral adrenal mass:
• Adenoma
• Carcinoma

Bilateral adrenal masses:
• BMAH
• PPNAD
• Bilateral cortisol-secreting adenomas

Definite pituitary tumor

If clinical picture fits with pituitary-dependent CS (eg, female, slow onset, mild to moderate CS, UFC <600 mcg) then IPSS usually not needed

Normal or equivocal MRI or picture "does not fit"

IPSS

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
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Serum DHEA-S

- 345 mcg/dL
(normal, 83-377 mcg/dL)

Cushing Syndrome

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- Head MRI
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- Treatment Menu

High Dose DST

- Not done

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
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- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

CRH Stimulation Test

- Not done

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
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- Monthly 24-hr UFCs
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- Midnight salivary F
- 1-mg overnight DST
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CXR

- Normal

Cushing Syndrome

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Head MRI

10 - 20% of normal individuals
have a ≥ 3 mm hypodense lesion



Clinical Context!

The pituitary MRI is normal in 50%
of patients with pituitary-dependent CS

Cushing Syndrome

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IPSS with CRH

- Not done

Cushing Syndrome

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- Treatment Menu

Chest CT/MRI

- Not done

Cushing Syndrome

Test Menu:

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- Treatment Menu

Adrenal CT/MRI

- Not done

Cushing Syndrome

Test Menu:

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- Adrenal CT/MRI
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- FDG-PET scan
- Treatment Menu

Octreotide/DOTATATE scans

- Not done

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
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FDG-PET Scan

- Not done

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Cushing Syndrome

Treatment Menu:

- Observation & re-evaluate in 3 to 6 mo
- Transsphenoidal surgery
- Unilateral adrenalectomy
- Bilateral adrenalectomy
- Resect ectopic ACTH tumor

Transsphenoidal Surgery

- “We then opened the dura and immediately found pituitary adenoma on the right side of the sella.”
- Immunohistochemistry + for ACTH pituitary tumor
- Serum cortisol:
 - ✓ 1 day postop = 2.4 $\mu\text{g}/\text{dL}$ (66.2 nmol/L)
 - ✓ 1 month postop = < 1.0 $\mu\text{g}/\text{dL}$

Approach to Glucocorticoid Taper*

- Home on prednisone 10-0-5-0 mg (if ectopic use higher dose), then drop total by 2.5 mg every 2 wks:
✓ 7.5-0-5-0 → 5-0-5-0 → 5-0-2.5-0 mg

Then substitute hydrocortisone (HC) 20 0 10 0 mg

This same approach is used for iatrogenic CS with taper and D/C of exogenous corticosteroids

10 0 10 0 / 7.5 0 5 0 / 5 0 5 0 mg

- Then, no further dosage taper; but rather check 8 AM cortisol before morning dose of HC every 6 wks
- When morning serum cortisol is >10 mcg/dL (>276 nmol/L), stop HC

*Hurtado MD, Cortes T, Natt N, Young WF Jr, Bancos I. Extensive clinical experience: Hypothalamic-pituitary-adrenal axis recovery after adrenalectomy for corticotropin-independent cortisol excess. *Clin Endocrinol (Oxf)*. 2018;89(6):721-733.

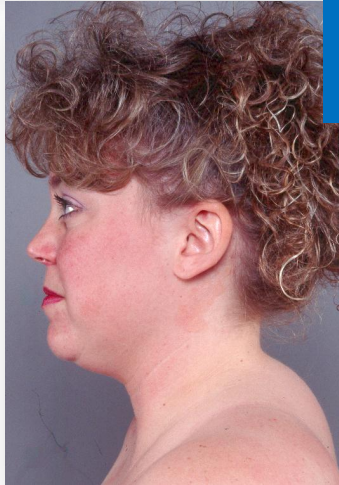
Preop



**6 months
Postop**



Q & A



**↑ BP resolved
↓ Wt 16#
Reg menses
↑ energy**

Case 2:

Cushing Syndrome: 41-Yr-Old Man

History of Present Illness:

- Referred for evaluation of “persistent Cushing syndrome after stopping prednisone”
- History of Crohn’s disease flare 1 yr ago – treated with prednisone until 6 mo ago (patient is uncertain of dose used)
- After stopping prednisone, his signs & sx related to prednisone therapy did not resolve
- Last month – his “prednisone symptoms” progressed

Case 2:

Cushing Syndrome: 41-Yr-Old Man

History of Present Illness (2):

- Last month— his “prednisone symptoms” ↑ed:
 - ✓ ↑ed fatigue; marked proximal muscle weakness
 - ✓ 50# wt gain; purple/red striae over the lower abd
 - ✓ New hypertension & diabetes mellitus
 - ✓ Scalp hair loss; rapid finger nail growth (clips every other day)
 - ✓ Hand tremor
 - ✓ Serum K⁺ was 1.7 mEq/L when Rx with HCTZ

Case 2:

Cushing Syndrome: 41-Yr-Old Man

History of Present Illness (3):

- No ETOH or tobacco
- **Meds:** Metoprolol (Lopressor®) 50 mg twice daily; Lisinopril (Prinivil/Zestril®) 20 mg twice daily; Amlodipine (Norvasc®) 10 mg once daily; Spironolactone (Aldactone®) 50 mg twice daily; Potassium chloride 20 mEq twice daily; Metformin (Glucophage®) 500 mg twice daily; 6-Mercaptopurine 50 mg tabs – 2 ½ tabs daily; Balsalazide (Colazal®) 750 mg – 3 tabs 3 times daily

41-Year-Old Man

Physical Exam:

- Ht = 172 cm,
Wt = 99.6 kg,
BMI = 33.7 kg/m²
- BP = 159/90 mmHg
HR = 74 bpm
- Plethoric face –
full, round, red;



41-Year-Old Man

Physical Exam:

- Central obesity
- Skin: red striae —
 • abdomen & axilla
 • supraclavicular
 • cervical fat pads
 • legs: minimal
 • lower extremity edema;
 • muscle



41-Year-Old Man

Laboratory tests:

- Hemoglobin = 14.0 gm/dL (N, 12.0 – 15.5)
- Sodium = 138 mEq/L (N, 135 – 145)
- Potassium = 4.4 mEq/L (N, 3.6 – 4.8)
- Calcium = 9.8 mg/dL (N, 8.9 – 10.1)
- Glucose = 133 mg/dL (N, 70 – 100)
7.4 mmol/L (N, 3.9 – 5.6)
- Uric acid = 4.1 mg/dL (N, 2.3 – 6.0)
- AST = 61 U/L (N, 12 – 31)
- Creatinine = 0.9 mg/dL (0.6 – 0.9)

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

Diurnal Serum Cortisols

- 8 a.m. = 27 $\mu\text{g/dL}$ (N < 25)
745 nmol/L (N < 690)
- 4 p.m. = 30 $\mu\text{g/dL}$ (N < 14)
828 nmol/L (N < 386)

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

24-Hour Urinary Free Cortisol

- 224 μg (N < 45)
618 nmol (N < 152)

Note: baseline 24-hr UFC prior to referral was 1,647 μg (4544 nmol)!!

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

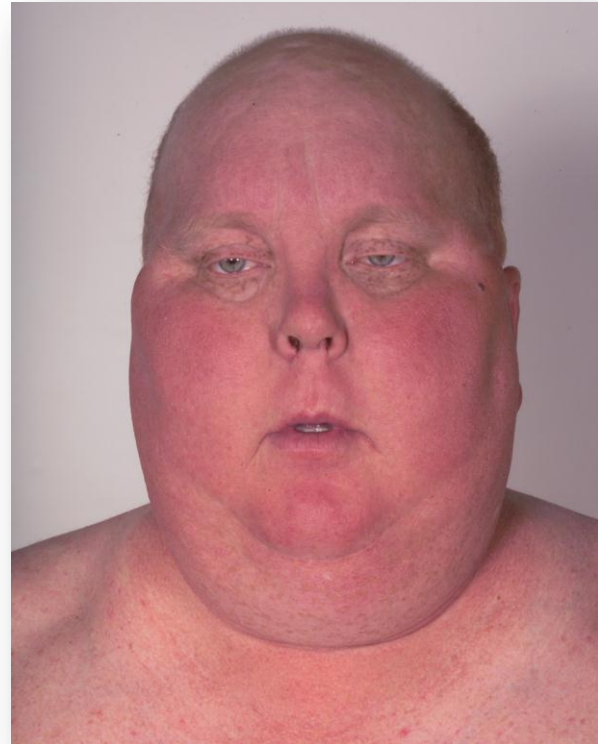
- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

Serial Patient Photos

3 years ago



Current



Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

Low-Dose DST

- Not done

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

Monthly 24-hr UFCs

- Not done

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

Dex-oCRH Test

- Not done

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

Midnight Salivary Cortisol

- 471 ng/dL (N <100)

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

1-mg Overnight DST

- Not done

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
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- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE
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- Treatment Menu

ACTH

- 93 pg/mL (N < 60)
20 pmol/L (N < 13)

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
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- Low-Dose DST
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- Treatment Menu

Serum DHEA-S

- 380 mcg/dL
(normal, 34-395 mcg/dL)

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
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- DHEA-S

- High-Dose DST
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- Chest XR
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- IPSS with CRH
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- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

High-Dose DST

- Not Done

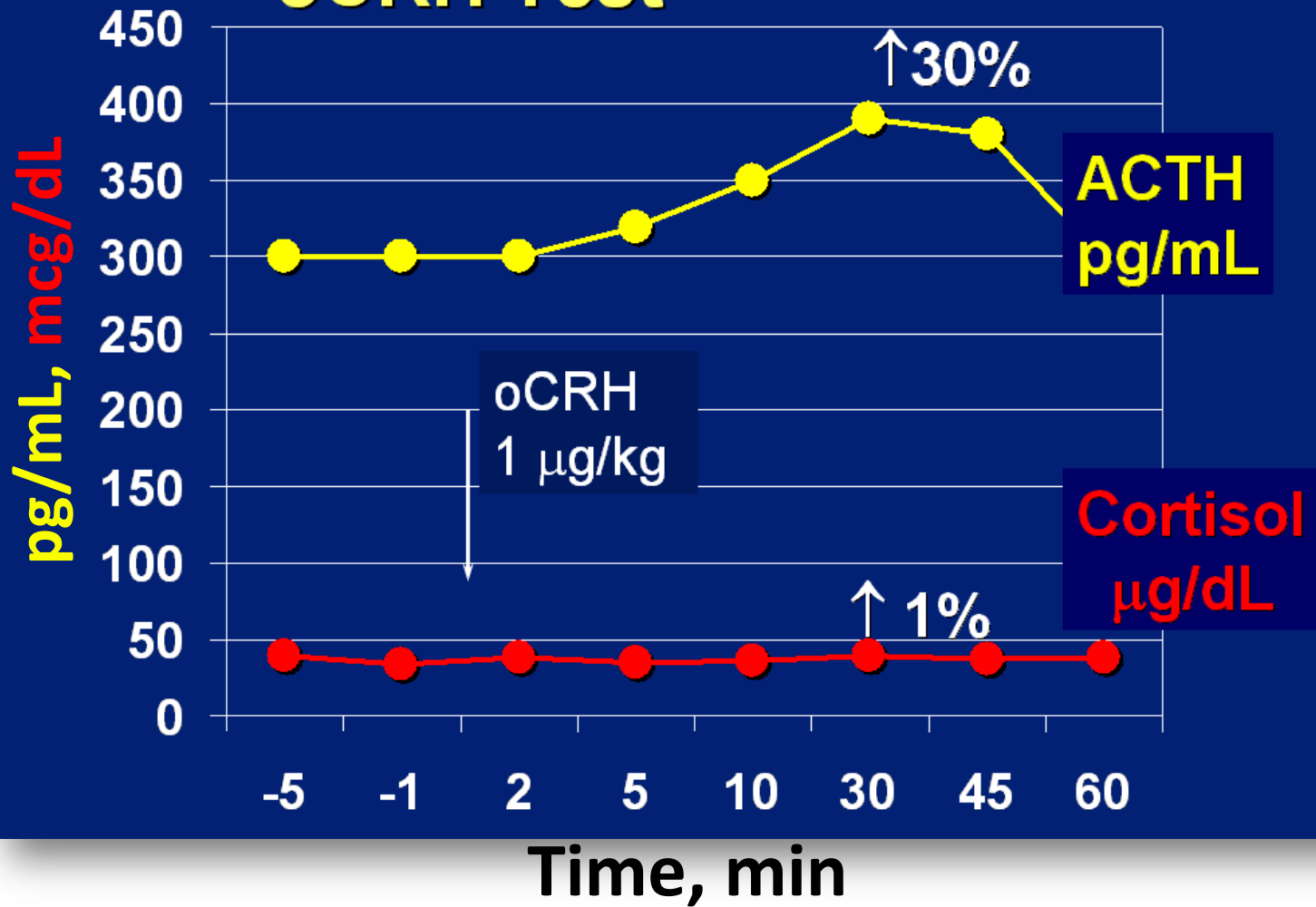
Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
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- Treatment Menu

oCRH Test



Cushing Syndrome

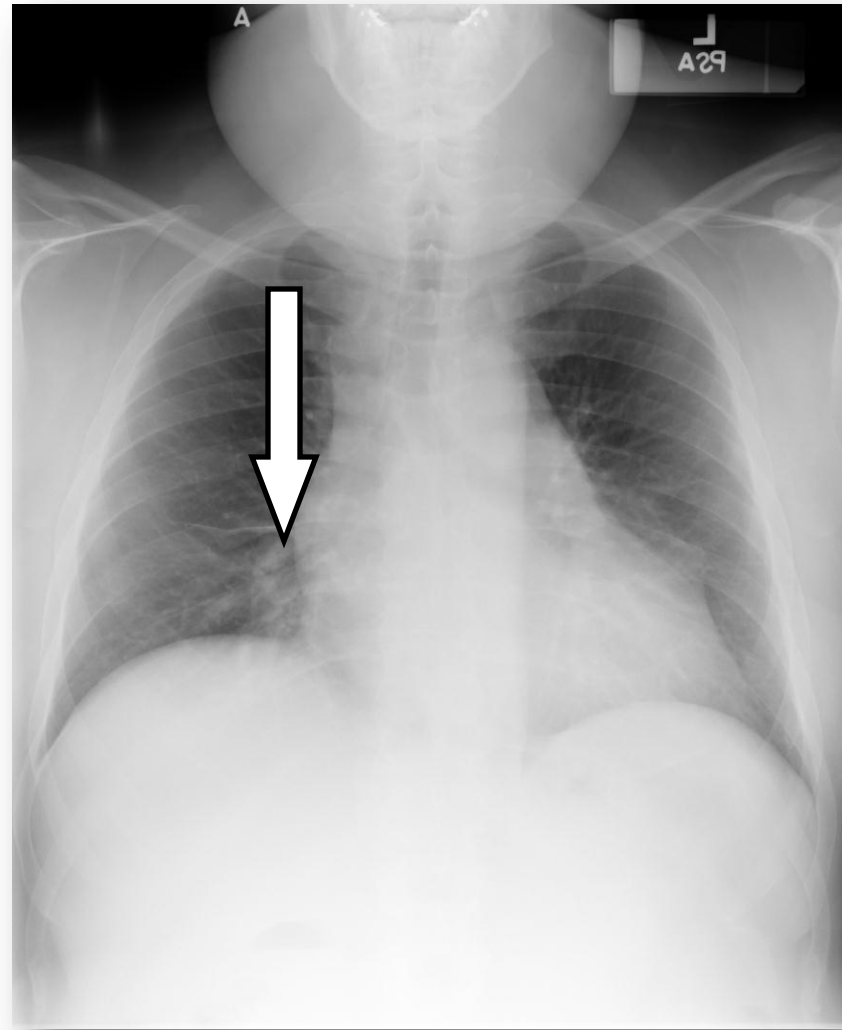
Test Menu:

- Diurnal serum cortisol
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Chest XR

“1-cm mass projected over the heart on lateral view may be in the RML or RML bronchus; fullness of anterior mediastinum may be due to fat”



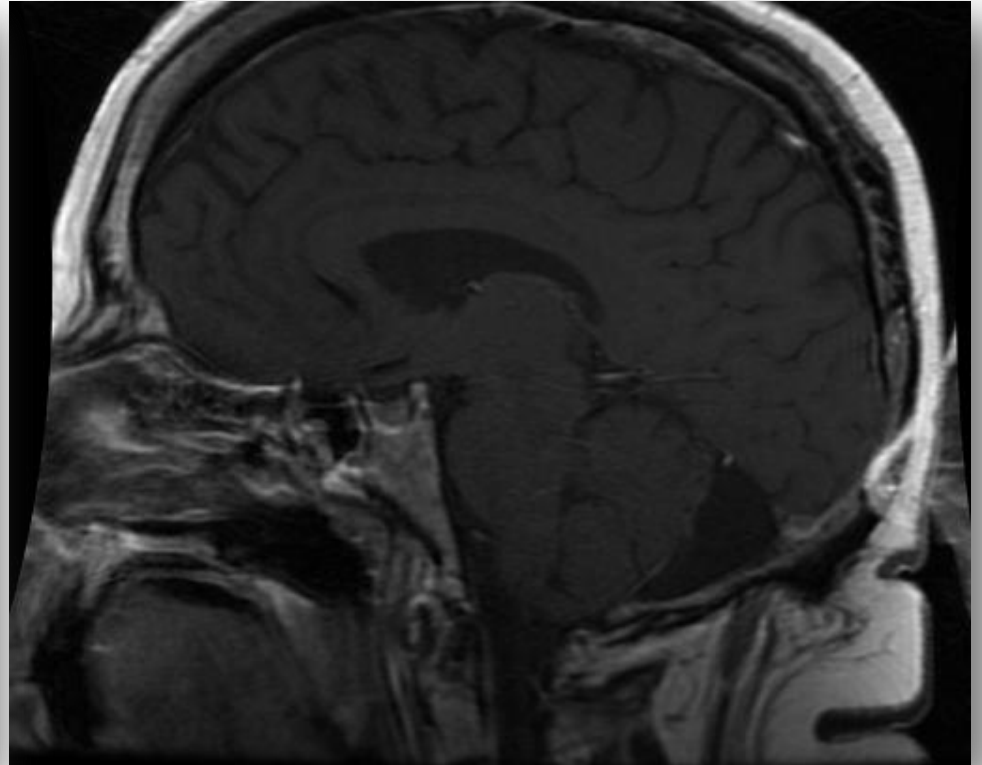
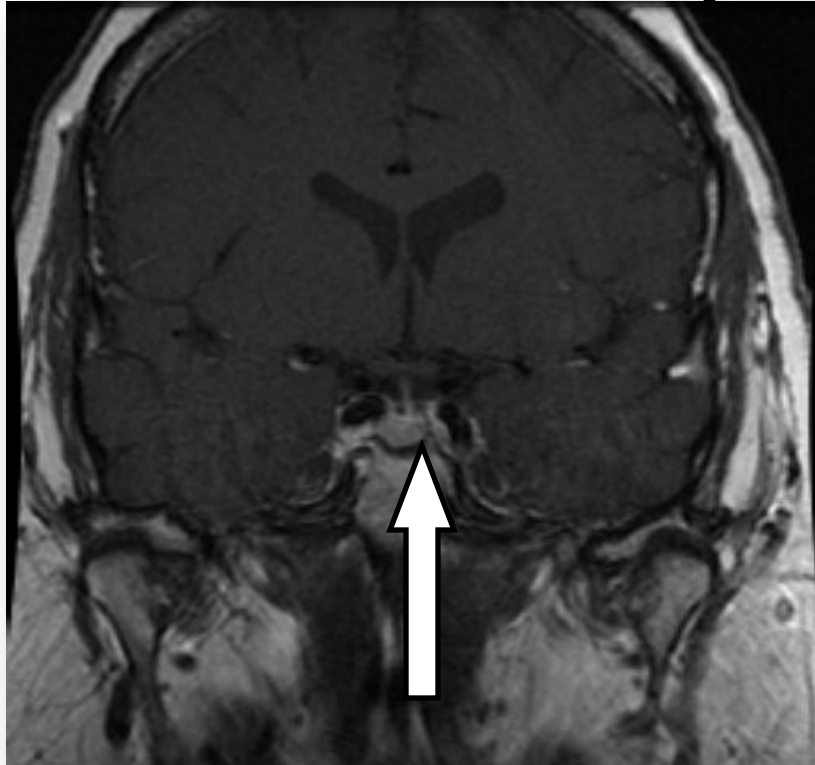
Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
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- High-Dose DST
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Head MRI “subtle 1.5 mm focus of T1 hypointensity on the LT suspicious for a microadenoma”



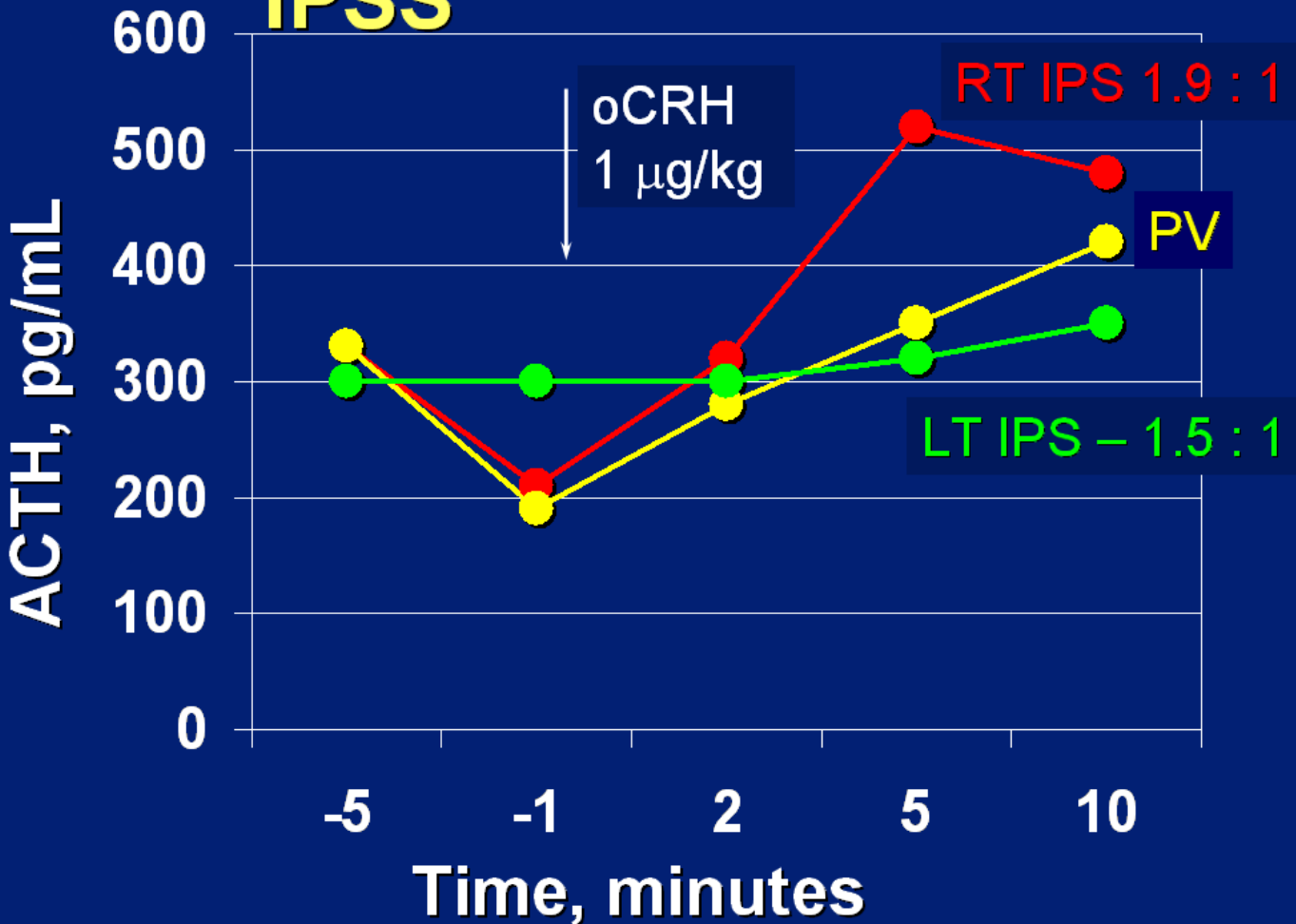
Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
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IPSS



RT IPS 1.9 : 1

PV

LT IPS - 1.5 : 1

oCRH
1 µg/kg

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
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- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

Chest MRI

“1.3-cm mass in the medial segment of the RML, which demonstrates mild enhancement on post-gad images”



Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

Adrenal CT

- Not Done

Cushing Syndrome

Test Menu:

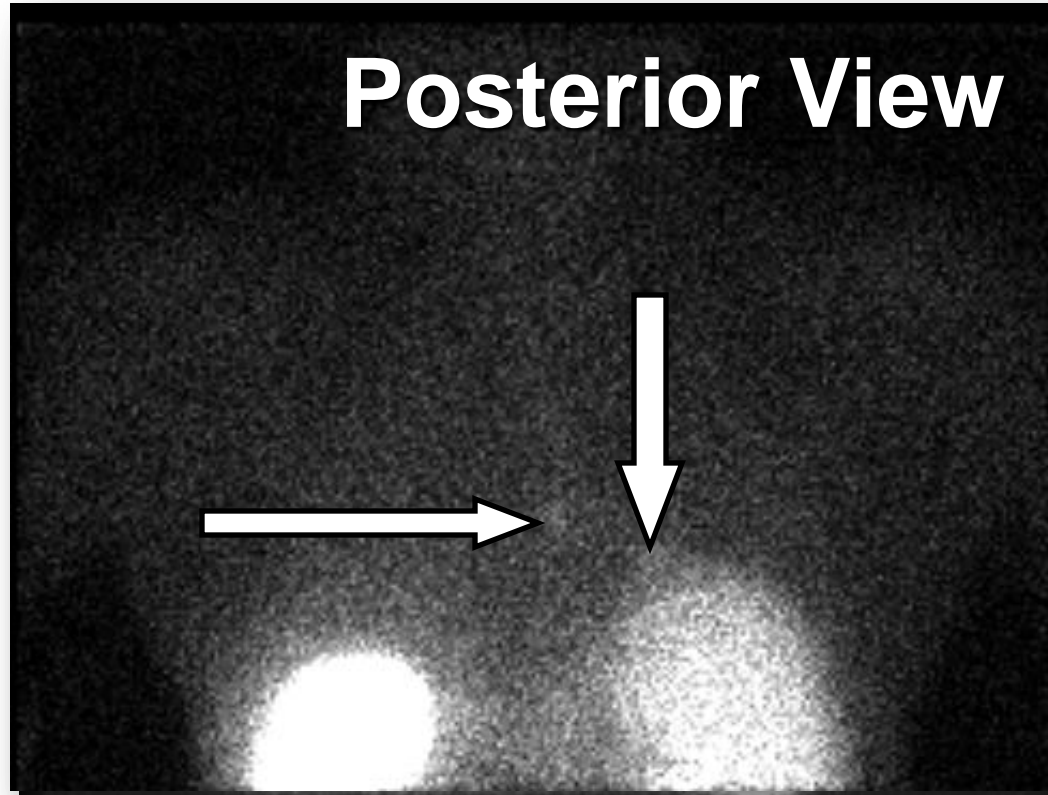
- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
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- Midnight salivary F
- 1-mg overnight DST
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- Treatment Menu

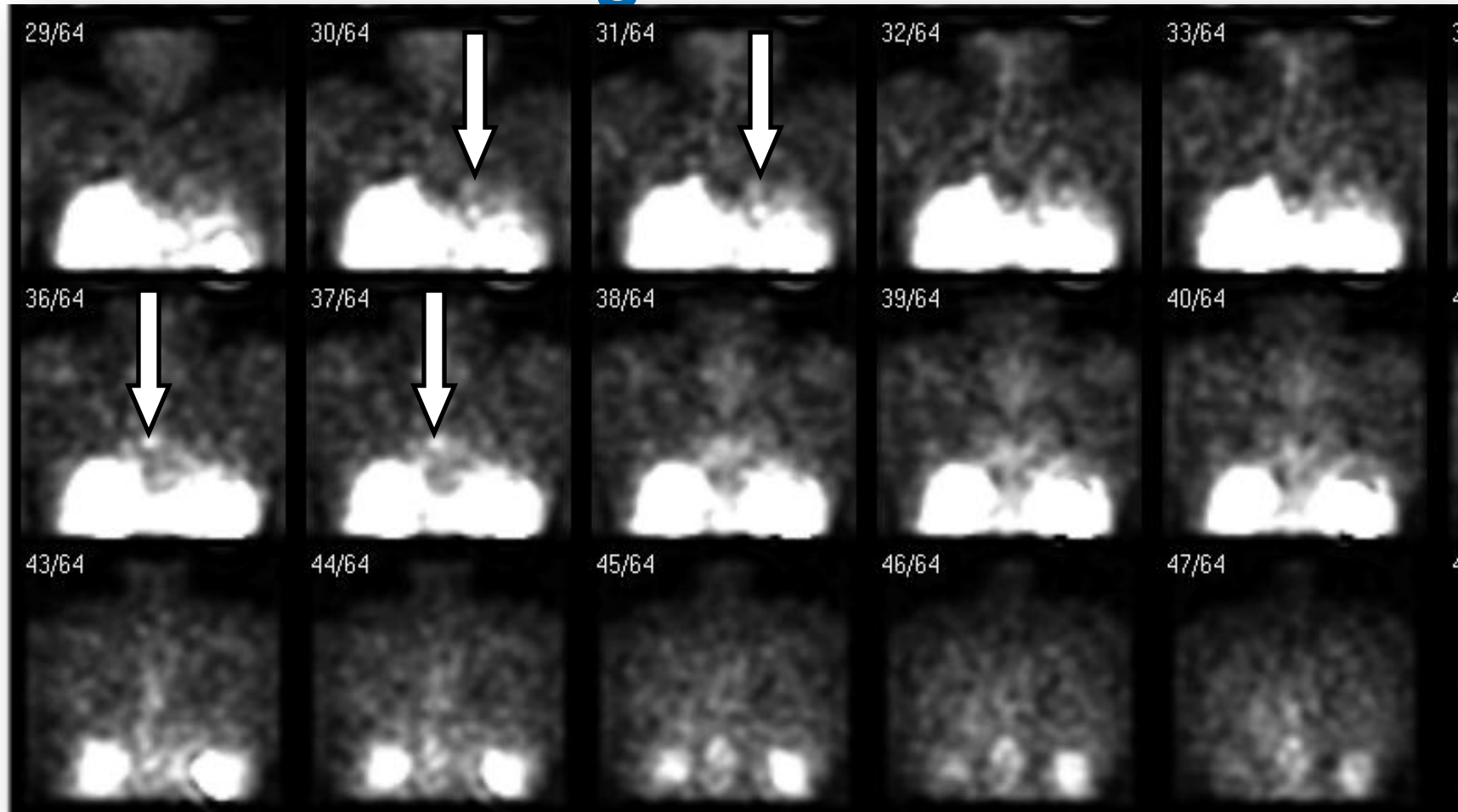
Octreotide Scan

“Focal uptake RT lung base, just medial to the dome of the liver”

“Additional focus slightly superior and in the midline – likely a subcarinal lymph node”



SPECT Images – Posterior View



Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
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- High-Dose DST
- CRH test
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- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

FDG-PET scan

- Not Done

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
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- Adrenal CT/MRI
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- FDG-PET scan
- Treatment Menu

Cushing Syndrome

Treatment Menu:

- Observation & re-evaluate in 3 to 6 mo
- Transsphenoidal surgery
- Unilateral adrenalectomy
- Bilateral adrenalectomy
- Resect ectopic ACTH tumor

RT Thoracotomy

- RT middle lobectomy
- Complete mediastinal lymphadenectomy
- Path: 1.7 x 1.4 x 1.4 cm carcinoid tumor; metastatic tumor involving 1 of 20 lymph nodes

Postoperative Course

1 Day Later:

- Cortisol = 3.2 $\mu\text{g/dL}$ (88.3 nmol/L)
- Dimitted from hospital on prednisone 10 mg twice daily;
KCL & spironolactone D/C

6 Weeks Later:

- Cortisol = 2.3 $\mu\text{g/dL}$ (63.5 nmol/L)
- Not tolerating prednisone taper

Postoperative Course

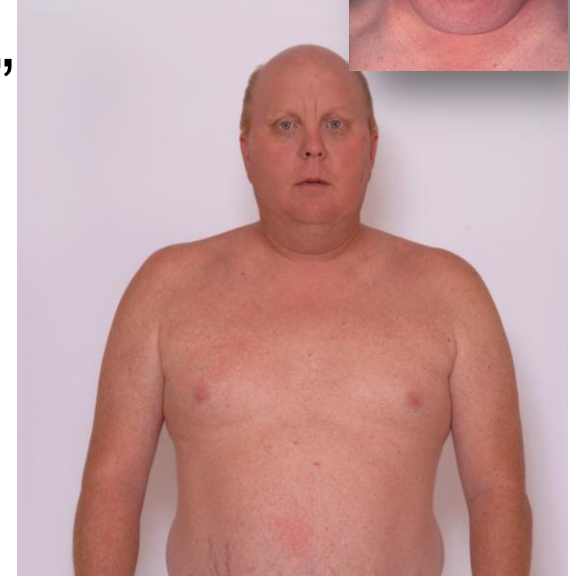
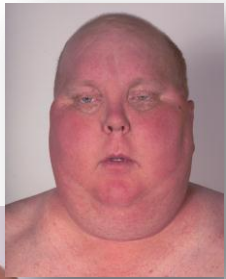
4 Months Later:

- Prednisone dose down to 5 mg twice daily
- ↓38 pounds; nl FPG and HbA1C – D/C metformin
- Low normal BP – cut back on BP meds
- Cortisol = 3.5 $\mu\text{g/dL}$ (97 nmol/L)
- Chest CT - NED

Postoperative Course

1 Year Later:

- Happy guy – “I’m back to my old self”
- Prednisone dose down to 5 mg every a.m.
- Has maintained wt loss
- BP still requires antihypertensive meds
- 8 a.m. cortisol prior to prednisone dose 8.7 mcg/dL



Q & A

Case #3: 20-Year-Old Woman

History of Present Illness:

- College student
- Hair thinning, easy bruising, facial flush, hair loss x 3 yr
- 2° amenorrhea x 6 mo; ↑BP x 3 mo
- Consulted with many MDs—no answer. Was visiting her Aunt—had not seen patient x 3 yrs—and her Aunt said “something must be wrong . . . she is losing her hair, she is weak, I even beat her in a 5K race along the Mississippi River”
- Meds: none

Case #3: 20-Year-Old Woman

Physical Exam:

- 165 cm, 57 kg,
BMI = 20.9 kg/m²
- BP 150/102 mm Hg
- Round, flushed face,
marked scalp hair loss,
small dorsocervical fat pad
striae on inner thighs
∴ consistent with mild CS



Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
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- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE scan
- FDG-PET scan
- Treatment Menu

Serum Cortisols

- 8 a.m. -- 23 $\mu\text{g/dL}$
(N < 25 $\mu\text{g/dL}$)
- 4 p.m. -- 22 $\mu\text{g/dL}$
(N < 14 $\mu\text{g/dL}$)

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
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- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
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- Adrenal CT/MRI
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- FDG-PET scan
- Treatment Menu

24-Hour Urinary Free Cortisol

- 24-hr UFC: 188 μg
(N < 45 μg)

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE scan
- FDG-PET scan
- Treatment Menu

Serial Photographs

- None

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE scan
- FDG-PET scan
- Treatment Menu

2-Day Low-Dose DST

- **24-hr UFC = 222 μg**

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE scan
- FDG-PET scan
- Treatment Menu

Monthly 24-hr UFC

- **Not done**

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE scan
- FDG-PET scan
- Treatment Menu

Dex-CRH Test

- Not Done

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
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- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE scan
- FDG-PET scan
- Treatment Menu

Midnight Salivary Cortisol x 2

- **Not done**

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
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- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE scan
- FDG-PET scan
- Treatment Menu

1-mg Overnight DST

- **Not done**

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
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- Treatment Menu

Serum ACTH

- **ACTH: < 5 pg/mL x 2**
(N < 50 pg/mL)

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
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- 1-mg overnight DST
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- Treatment Menu

Serum DHEA-S

- **DHEA-S: <15 $\mu\text{g}/\text{dL}$**
(N, 44 - 332 $\mu\text{g}/\text{dL}$)

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
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- Treatment Menu

High Dose DST

- **8 mg overnight DST: 8 a.m.
cortisol = 23 $\mu\text{g/dL}$
(normal $<1 \mu\text{g/dL}$)**

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
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- Treatment Menu

CRH Stimulation Test

- Not done

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
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- Low-Dose DST
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- Treatment Menu

CXR

- Normal

Cushing Syndrome

Test Menu:

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- Treatment Menu

Head MRI

- Not Done

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
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- Treatment Menu

IPSS with CRH

- Not done

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE scan
- FDG-PET scan
- Treatment Menu

Chest CT/MRI

- Not done

Cushing Syndrome

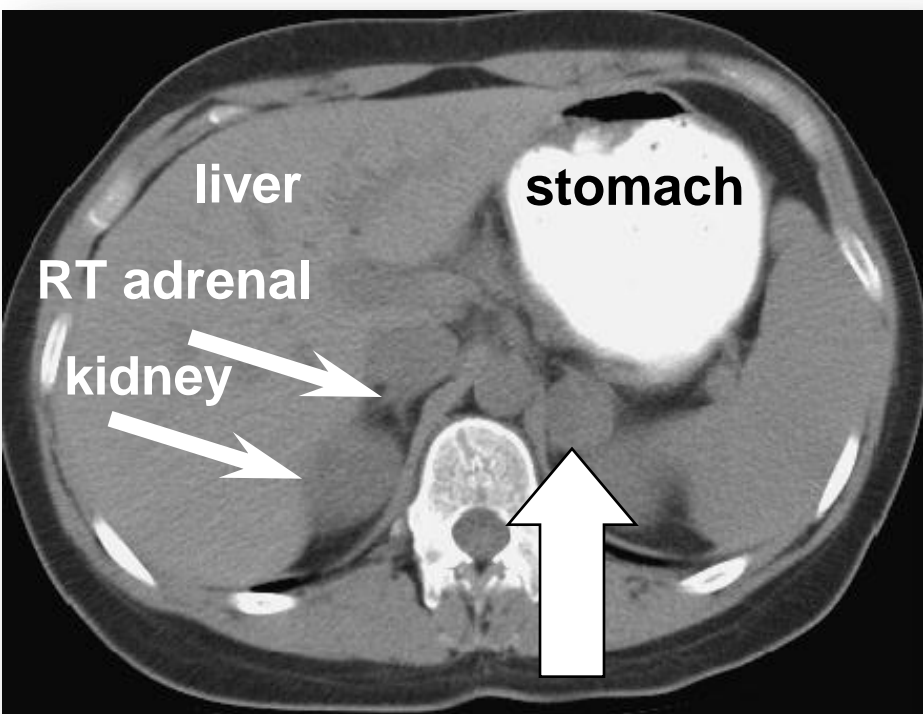
Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
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- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
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- DHEA-S

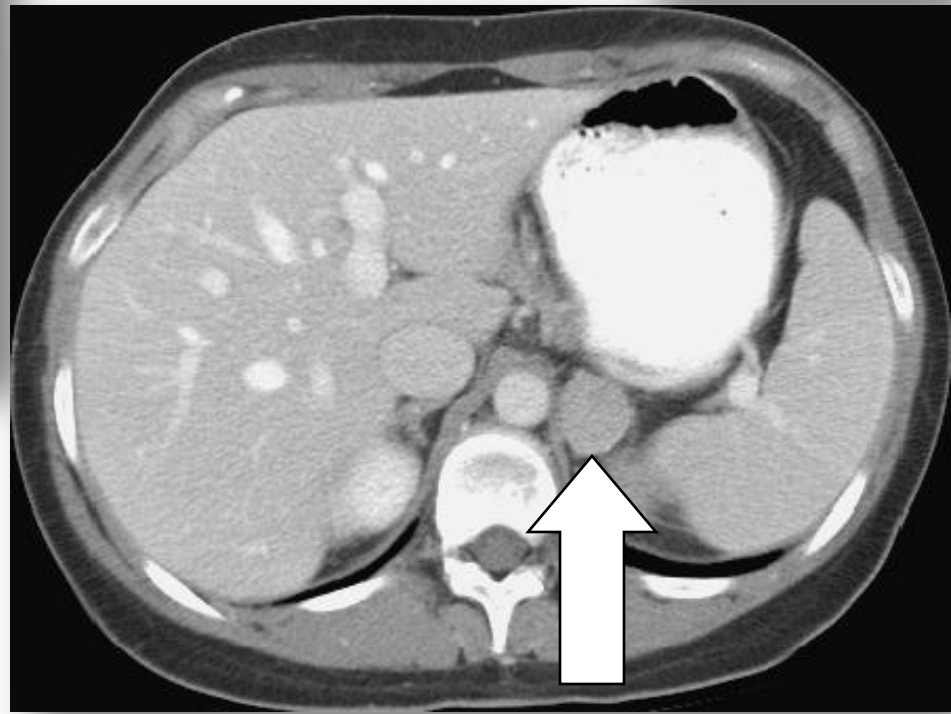
- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE scan
- FDG-PET scan
- Treatment Menu

Adrenal CT/MRI

- Yes, done!



2.5 x 2.5 cm lipid poor adrenal mass (unenhanced CT attenuation = 26 HU)



Cushing Syndrome

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- CRH test
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- IPSS with CRH
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- Octreotide/DOTATATE scan
- FDG-PET scan
- Treatment Menu

Octreotide/DOTATATE

- Not done

Cushing Syndrome

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- FDG-PET scan
- Treatment Menu

FDG-PET Scan

- Not done

Cushing Syndrome

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- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE scan
- FDG-PET scan
- Treatment Menu

Cushing Syndrome

Treatment Menu:

- Observation & re-evaluate in 3 to 6 mo
- Transsphenoidal surgery
- Unilateral adrenalectomy
- Bilateral adrenalectomy
- Resect ectopic ACTH tumor

Adrenalectomy

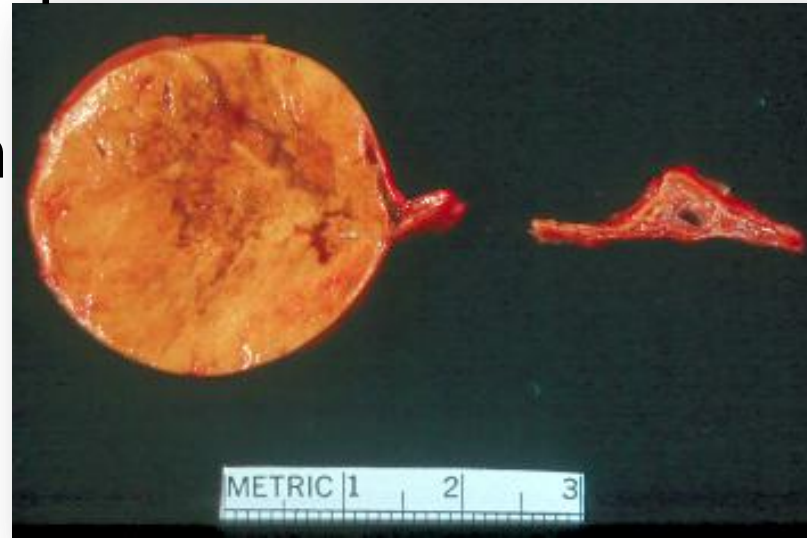
Q & A



- “two left adrenal veins . . . clipped and divided . . . specimen removed and placed in endobag & removed through epigastric port”

- Pathology: 9 gm; 2.4 x 2.4 x 2.4 cm cortical adenoma with surrounding cortical atrophy

- Follow-up:
Postop cortisol = 0
signs & sx resolved
exogenous glucocorticoids D/C 1 yr later



Case #4: 46-Year-Old Woman

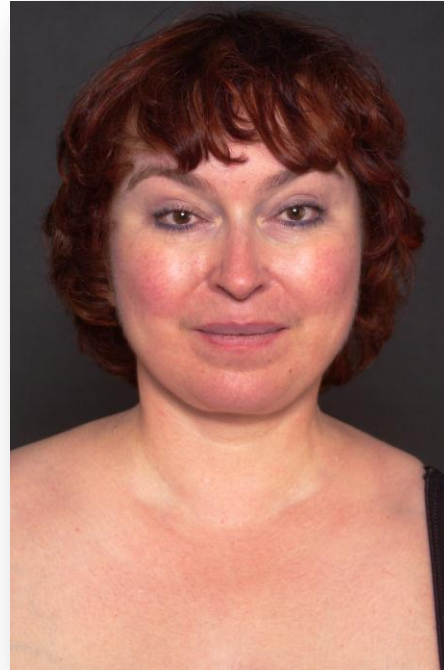
History of Present Illness:

- New onset ↑BP, wt gain, easy bruising
- Muscle weakness (stairs)
- Normal menses & normal BMD
- Main concerns are fluid retention & wt gain (83 kg to 103 kg over 4 yr)—spa treatments, liposuction, & herbals all ineffective
- Meds: irbesartan/HCTZ, torsemide

Case #4: 46-Year-Old Woman

Physical Exam:

- 175 cm, 103 kg,
BMI = 33.5 kg/m²
- BP 160/90 mm Hg
- Full face, no hirsutism
no striae
proximal muscle weakness
edema—ankles bilat



Cushing Syndrome

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- Treatment Menu

Serum Cortisols

- 8 a.m. -- 16 $\mu\text{g}/\text{dL}$
(N < 25 $\mu\text{g}/\text{dL}$)
- 4 p.m. -- 16 $\mu\text{g}/\text{dL}$
(N < 14 $\mu\text{g}/\text{dL}$)

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
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- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
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24-Hour Urinary Free Cortisol

- 24-hr UFC: 275 μg (N < 45 μg)

Cushing Syndrome

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- 1-mg overnight DST
- ACTH level
- DHEA-S

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1977



1996



1994



1996



1998



1998



2000



2000



Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
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- High-Dose DST
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- Treatment Menu

2-Day Low-Dose DST

- **Not Done**

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

Monthly 24-hr UFC

- **Not done**

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

Dex-CRH Test

- Not Done

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

Midnight Salivary Cortisol x 2

- **Not done**

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
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- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

1-mg Overnight DST

- **Not done**

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
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- Midnight salivary F
- 1-mg overnight DST
- ACTH level
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- High-Dose DST
- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide/DOTATATE
- FDG-PET scan
- Treatment Menu

Serum ACTH

- **ACTH: < 5 pg/mL x 2**
(N < 50 pg/mL)

Cushing Syndrome

Test Menu:

- Diurnal serum cortisol
- 24-hr UFC
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- Chest CT/MRI
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- Treatment Menu

Serum DHEA-S

- **DHEA-S: < 15 $\mu\text{g}/\text{dL}$**
(N, 18 - 244 $\mu\text{g}/\text{dL}$)

Cushing Syndrome

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High Dose DST

- **8 mg overnight DST: 8 a.m.
cortisol = 28 μ g/dL**

Cushing Syndrome

Test Menu:

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CRH Stimulation Test

- Not done

Cushing Syndrome

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- Low-Dose DST
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CXR

- Normal

Cushing Syndrome

Test Menu:

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Head MRI

- Not Done

Cushing Syndrome

Test Menu:

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IPSS with CRH

- Not done

Cushing Syndrome

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- Treatment Menu

Chest CT/MRI

- Not done

Cushing Syndrome

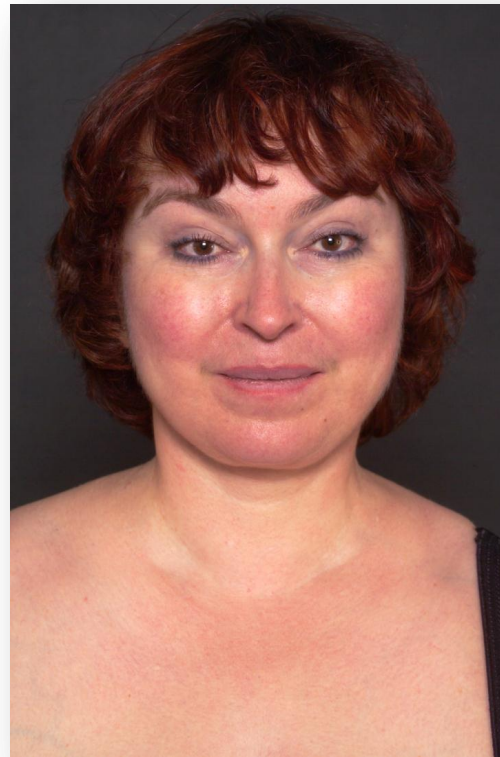
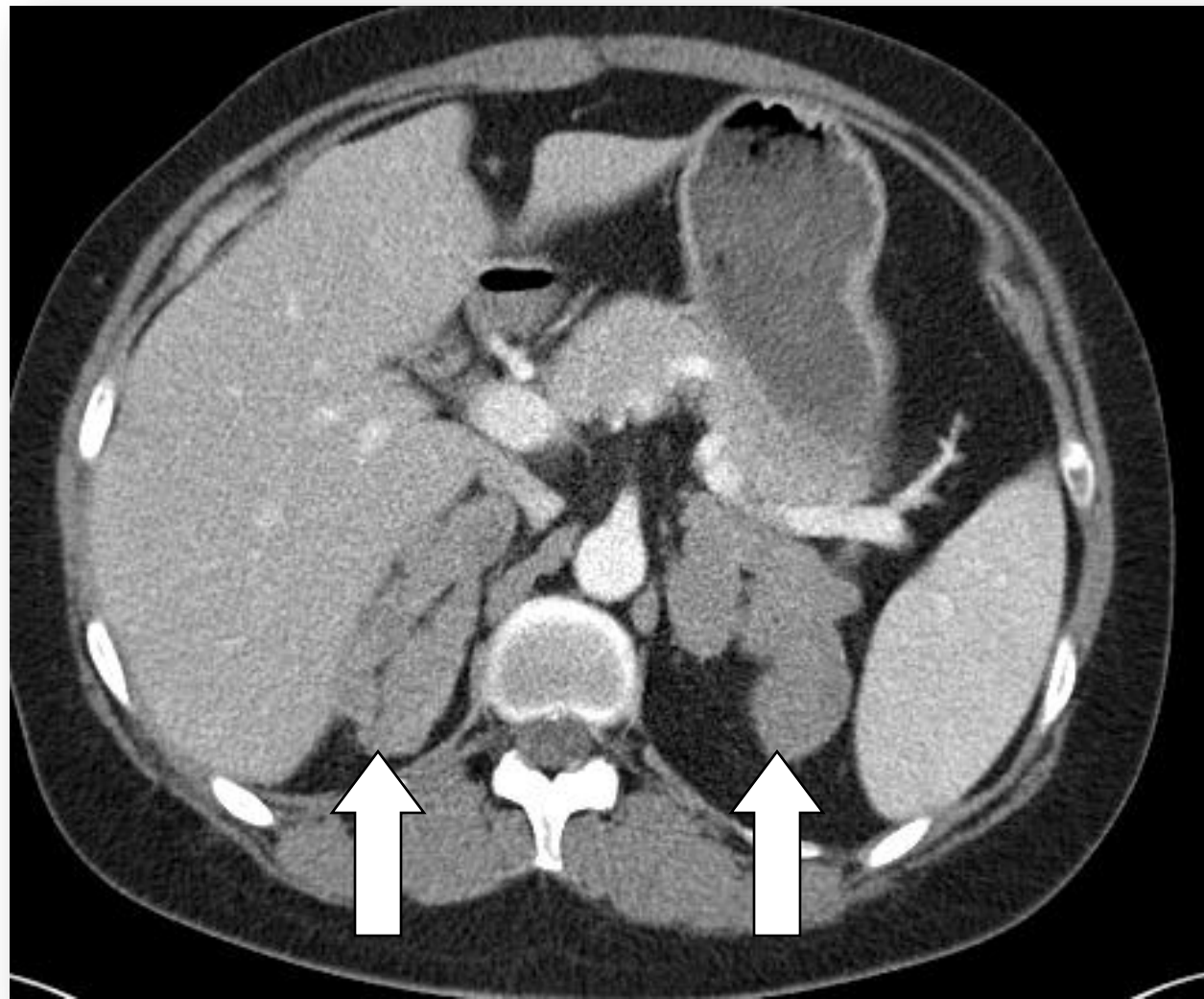
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Adrenal CT/MRI

- Yes, done!



Cushing Syndrome

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- Treatment Menu

Octreotide/DOTATATE scan

- Not done

Cushing Syndrome

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- Treatment Menu

FDG-PET Scan

- Not done

Cushing Syndrome

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- FDG-PET scan
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Cushing Syndrome

Treatment Menu:

- Observation & re-evaluate in 3 to 6 mo
- Transsphenoidal surgery
- Unilateral adrenalectomy
- Bilateral adrenalectomy
- Resect ectopic ACTH tumor

Lap LT Adrenalectomy

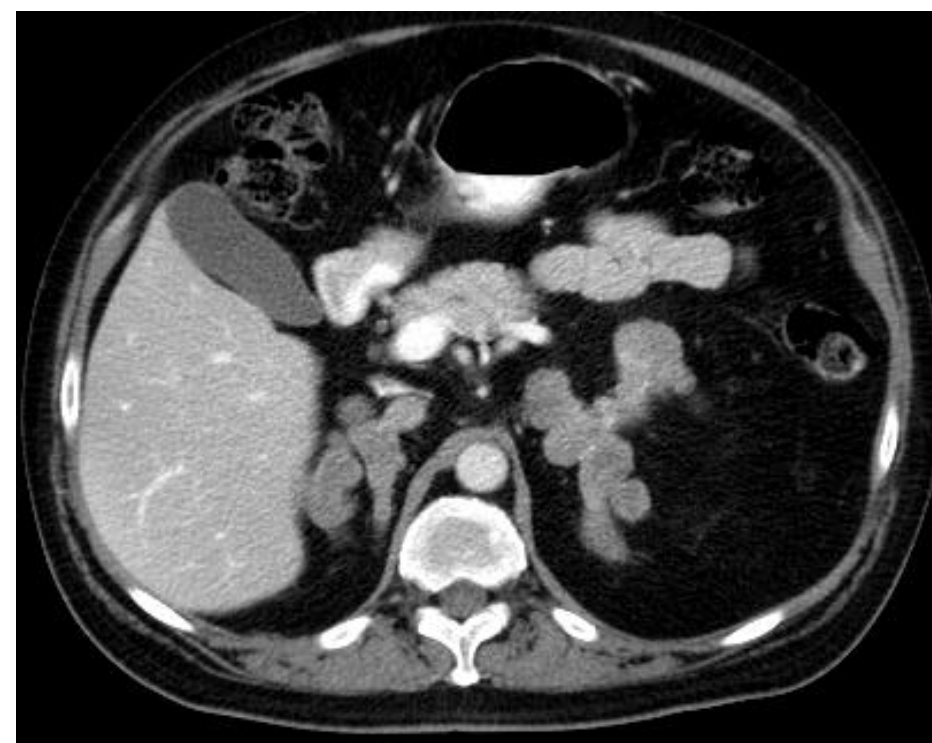
- “adrenal gland was massively enlarged and macronodular in appearance . . . Once the gland was freed, it was removed in a large endo catch bag after e
- Pathology:
205 gm, 15 x 7.8
macronodular
adrenal cortical
hyperplasia

PBMAH – frequently genetic:

Constitutive inactivating variants:

- tumor suppressor gene armadillo repeat containing 5 (*ARMC5*)—25% of PBMAH cases

- lysine (K)-specific demethylase (*KDM1A*)—90% of food-dependent CS PBMAH cases



CT signature of PBMAH – this can be nothing else!

Follow-up—1 month:

- 24-hr UFC: 200 μg (N < 45 μg)
- Advised to take ketoconazole until she returns for completion adrenalectomy

Q & A

3 years later:

- Lap RT adx
- CS cured:
 - ✓ 26 kg weight loss

Final Thoughts

Pace of Evaluation:

- If the symptoms are mild and biochemical tests borderline, take your time—the goal is NOT to correct laboratory values, but rather to treat signs and symptoms of CS—if you are having trouble confirming CS, there is no RUSH!
- If the patient has severe ACTH-dependent CS and source of ACTH is not evident, don't waste time—send them to bilateral laparoscopic adrenalectomy!

Final Thoughts

- There is no “one” algorithm for the diagnosis or the subtype evaluation
- The clinical features dictate the tests for confirmatory and subtype evaluation
- No biochemical test should “over rule” clinical intuition!
- A **man** with ACTH-dependent CS – think ectopic
- A **woman** with slowly developing and mild to moderate ACTH-dependent CS – almost certainly pituitary tumor
- IPSS is needed in a minority of patients with pituitary-dependent disease



Cushing Syndrome MTP

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Tyson Family Endocrinology Clinical Professor
Mayo Clinic, Rochester, MN USA

Day 1 – 27th August – 4:15 – 5:15 PM