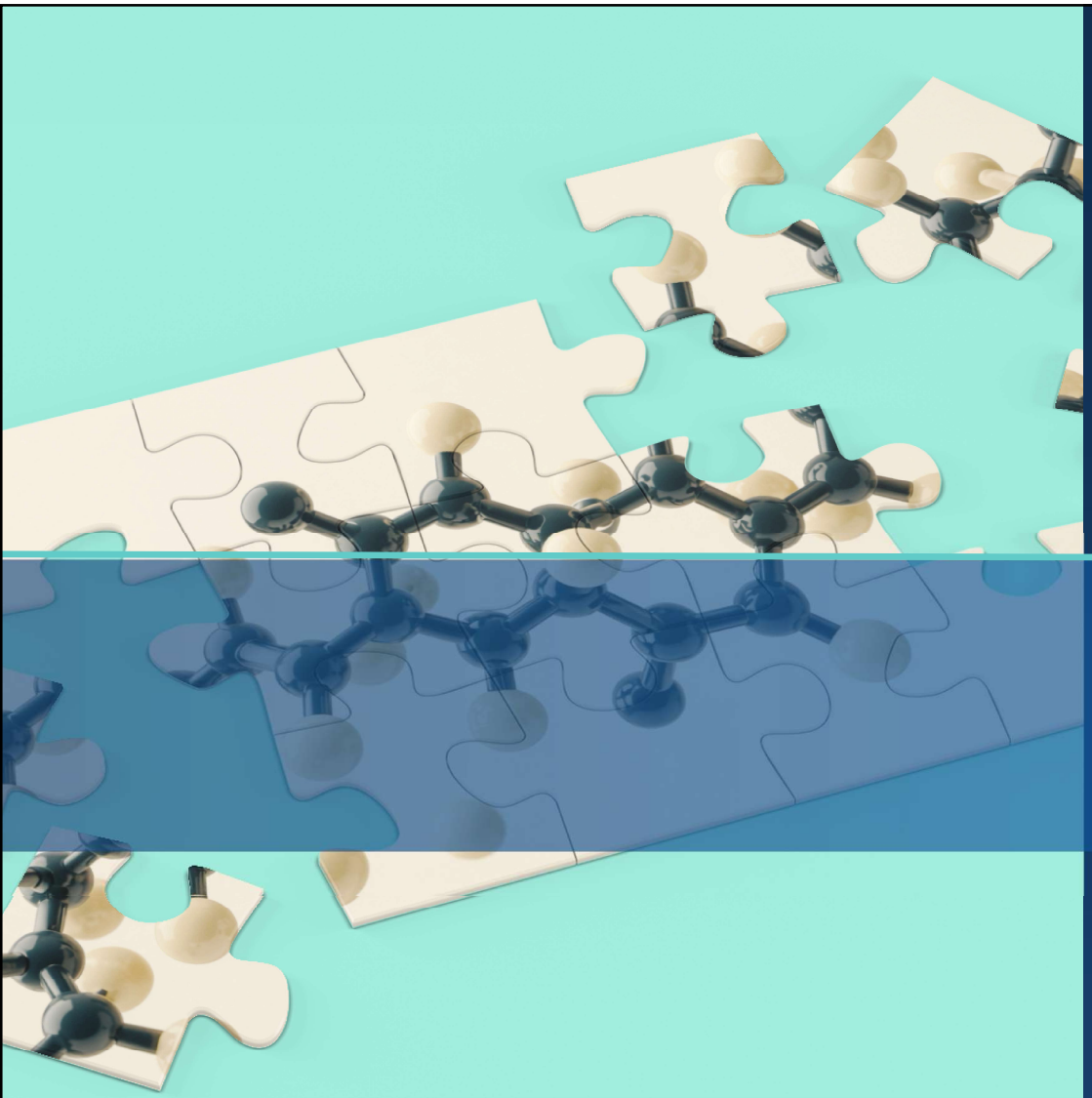

Cortisol Case Challenges

Patient Case Review for Effective Identification and Management of Cushing Syndrome

Presented by

Cornerstone Medical Education

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Supported by an educational grant from Corcept Therapeutics

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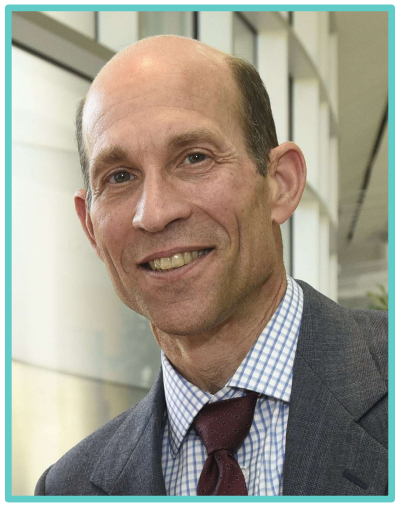

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Disclosures

Faculty Disclosures

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- Richard J. Auchus, MD, PhD, FACE (Faculty):
  - Advisory Board/Consultant: Quest Diagnostics, Corcept Therapeutics, Xeris Pharmaceuticals, Crinetics Pharmaceuticals, Novo Nordisk, Neurocrine Biosciences & Neurocrine UK, LTD, Recordati Rare Diseases, H Lundbeck A/S, Sparrow Pharmaceuticals, Astellas Pharmaceuticals, Acerand Therapeutics, OMass Therapeutics, Blue Earth Diagnostics, LTD, Spruce Biosciences, Aspect Biosystems, Merck Sharp & Dohme, LLC, Vertex Pharmaceuticals; Grant/Research Support: Neurocrine Biosciences, Neurocrine UK, LTD, Spruce Biosciences, Corcept Therapeutics, Crinetics Pharmaceuticals, Recordati Rare Diseases, Adrenas Therapeutics, Mineralys Pharmaceuticals, H Lundbeck A/S

Planner/Reviewer Disclosures

- Amy Burmesch, PA-C (Reviewer): Speaker's Bureau: Corcept Therapeutics
- Skand Shekhar, MD, MHSc (Reviewer) has no relevant relationships to disclose.
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See the Activity Description Page for information about credits offered for this activity.

Learning Objectives

- Develop individualized, evidence-driven medical management plans for patients with Cushing Syndrome.
- Apply the principles of shared decision-making and team-based care to real-world patient cases, focusing on initial treatment and monitoring/follow-up of patients with Cushing Syndrome.

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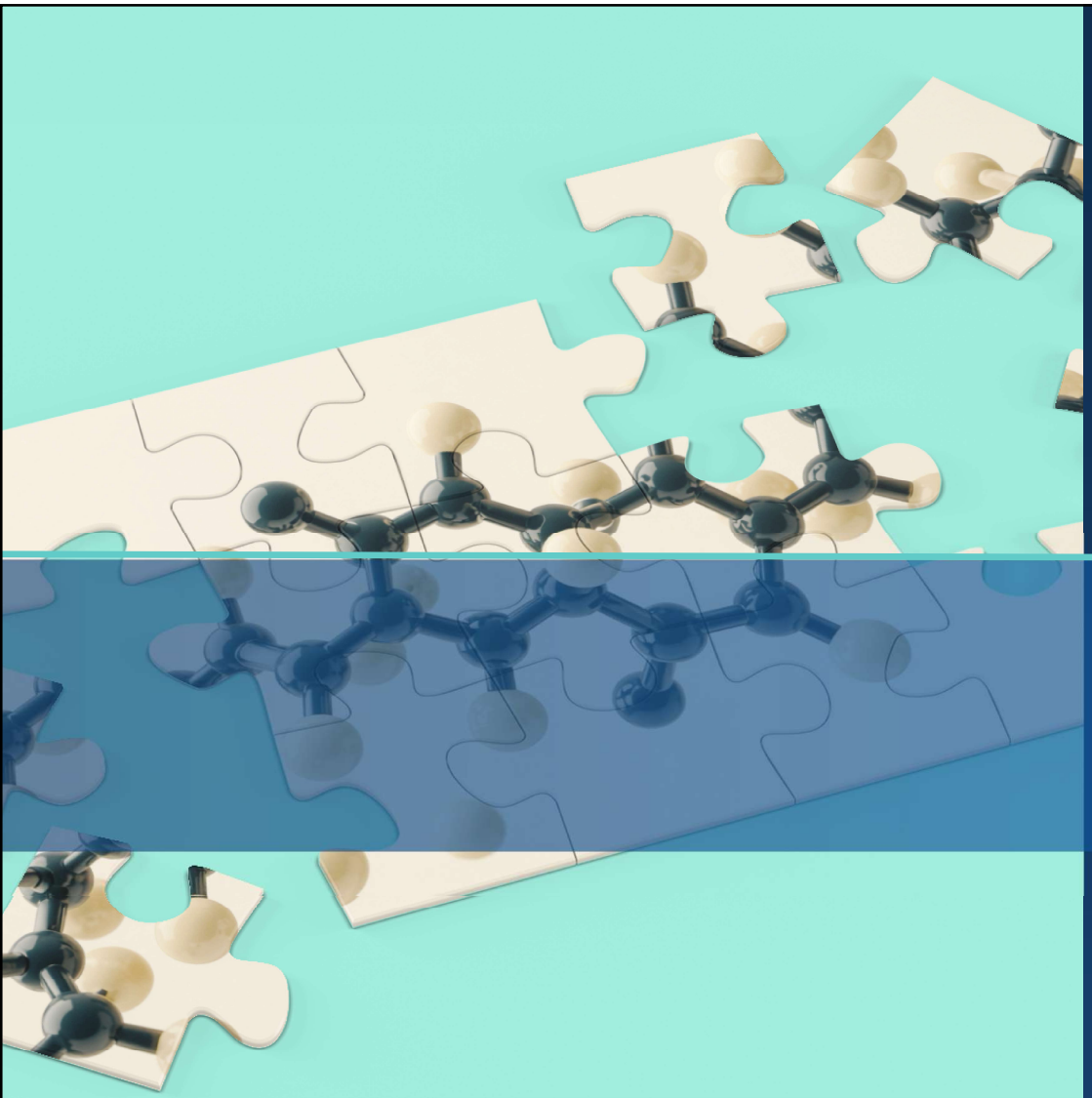


Cortisol Case Challenges

Patient Case Review for Effective Identification and Management of Cushing Syndrome

Hypercortisolism/Cushing Syndrome

Review of Part 1

- High Index of Suspicion
  - Diabetes, Hypertension, Osteoporosis, Treatment Resistance
- Increased Morbidity & Mortality From Any Severity
- Forms of Hypercortisolemia
  - ACTH-Dependent: Cushing Disease, Ectopic ACTH; Rare
  - ACTH-Independent: Adrenal Tumors; Not Rare
  - Non-Neoplastic: Chronic Illness, Stress; Common
- Surgery is Primary Treatment of Neoplastic CS
- Medical Therapy When Surgery Ineffective
  - Pros & Cons of Each Drug

Cushing Syndrome Features

Specific Features

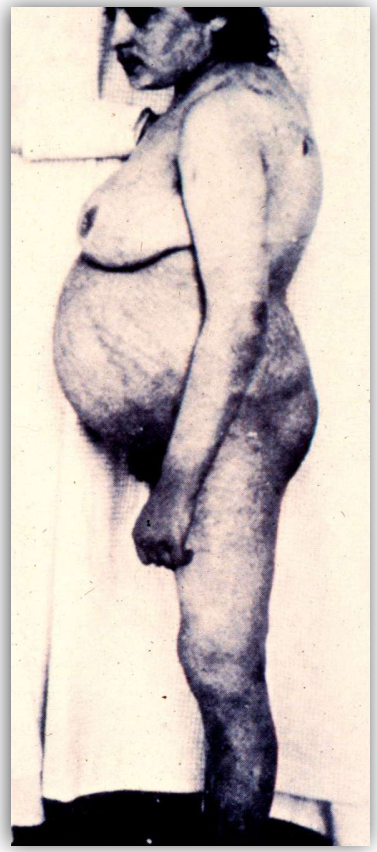
- Proximal Muscle Weakness/Myopathy
- Osteoporosis
- Wide, Purple, Non-blanching Striae
- Easy Bruising Without Anticoagulant Therapy

Common Less Specific Findings

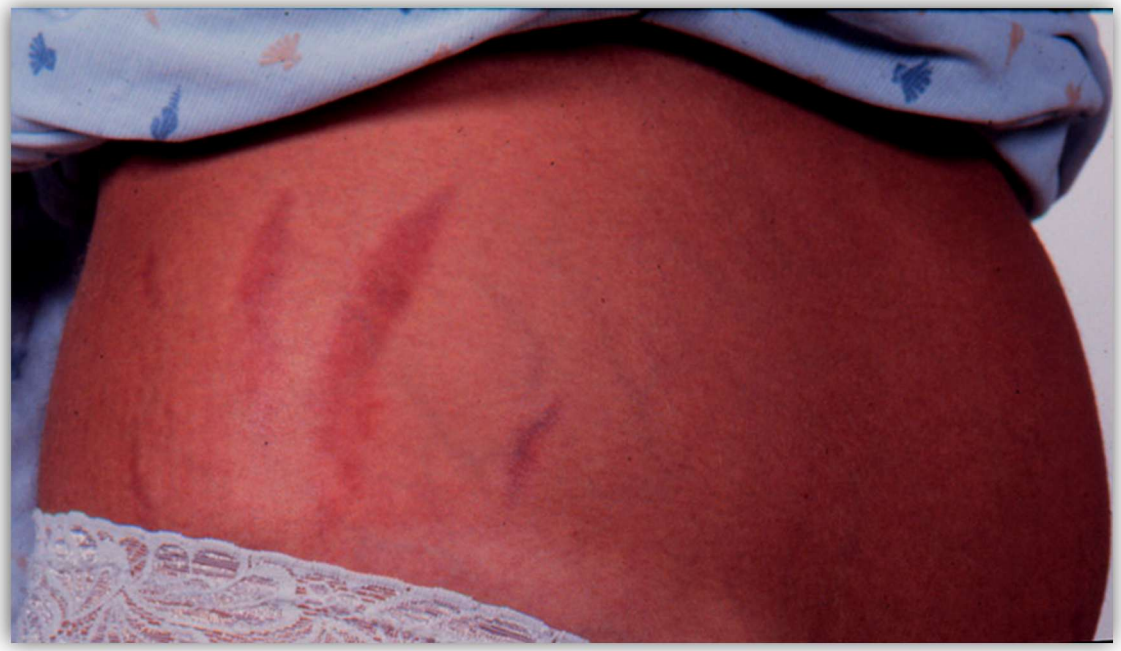
- Dermal Atrophy
- Disproportionate Head & Neck (SC/DC) Fat
- Poor Sleep
- Unexplained Hyperglycemia/HTN/Bone Loss

Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2021; Gadelha M, et al. *Lancet*. 2023; Nieman LK, et al. *J Clin Endocrinol Metab*. 2015.

Classical Cushing Syndrome



- **Specific Overt Physical Findings & Stigmata**
- **Rare Disease 1:10,000-100,000**
- Majority are ACTH-Dependent, Pituitary > Ectopic



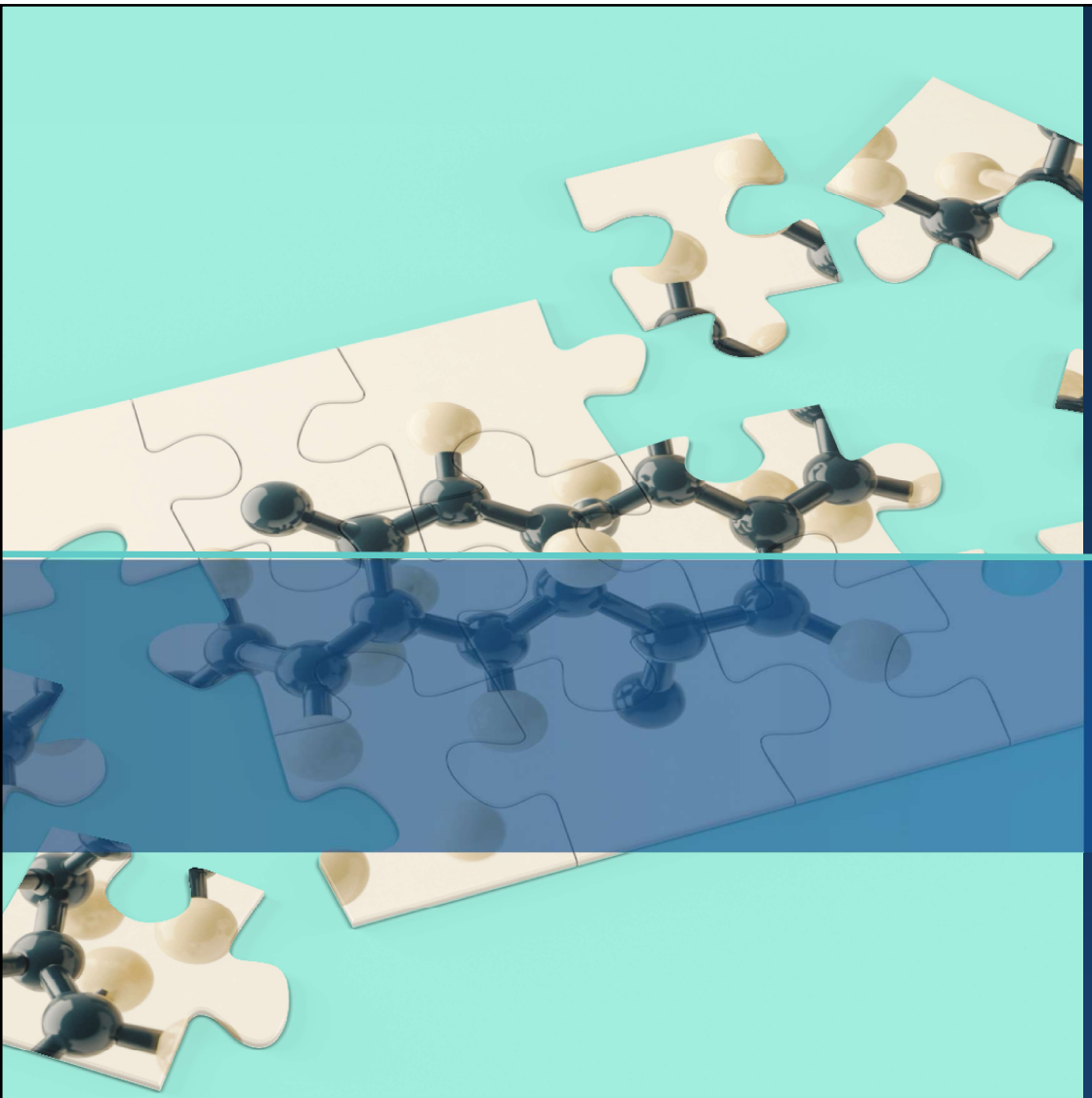
1995

2003

Hypercortisolemia
Principles of Testing

- Cortisol Production is Elevated
  - Urinary Free Cortisol
  - Not Always High, Varies With Assay
- Cortisol Production is Not Suppressible
  - Dexamethasone Suppression
  - Most Sensitive for ACTH-Independent
- The Diurnal Rhythm is Blunted
  - Nocturnal Serum or Saliva Cortisol
  - Saliva Cortisol Now Routine

Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2021; Gadelha M, et al. *Lancet*. 2023; Nieman LK, et al. *J Clin Endocrinol Metab*. 2015.



Case 1

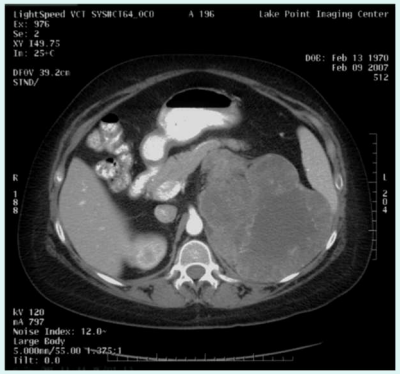
37yr old female with abdominal pain

Case 1 Presentation

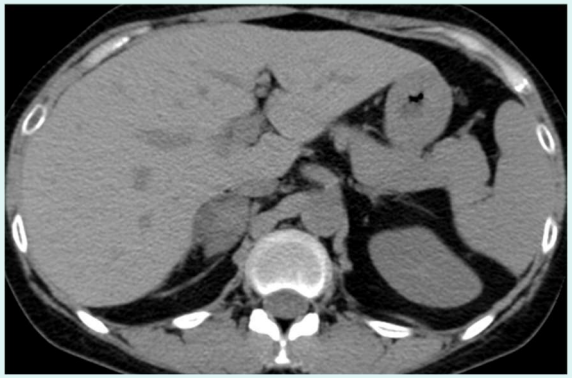
- 37 years old WF, New Onset HTN, Impaired Fasting Glucose
- CT for Abdominal Pain: 2.3 cm Left Adrenal Mass
- ROS: Mild Weight Gain, Regular Menses
- PE: Mild Suggestive Features – Facial Plethora, Moon Facies, Dermal Atrophy, SC Fat Pads, Central Obesity

ACTH-Independent Hypercortisolemia

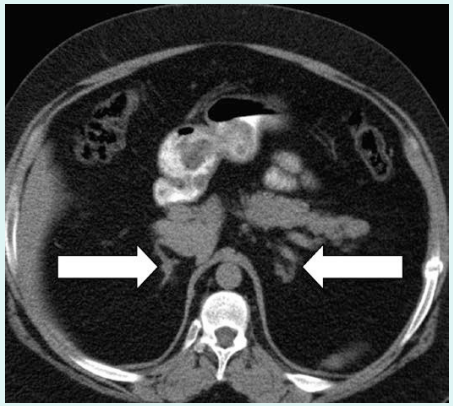
Adrenocortical Carcinoma



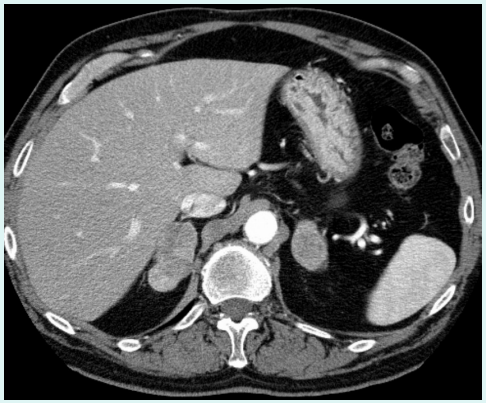
Adrenocortical Adenoma



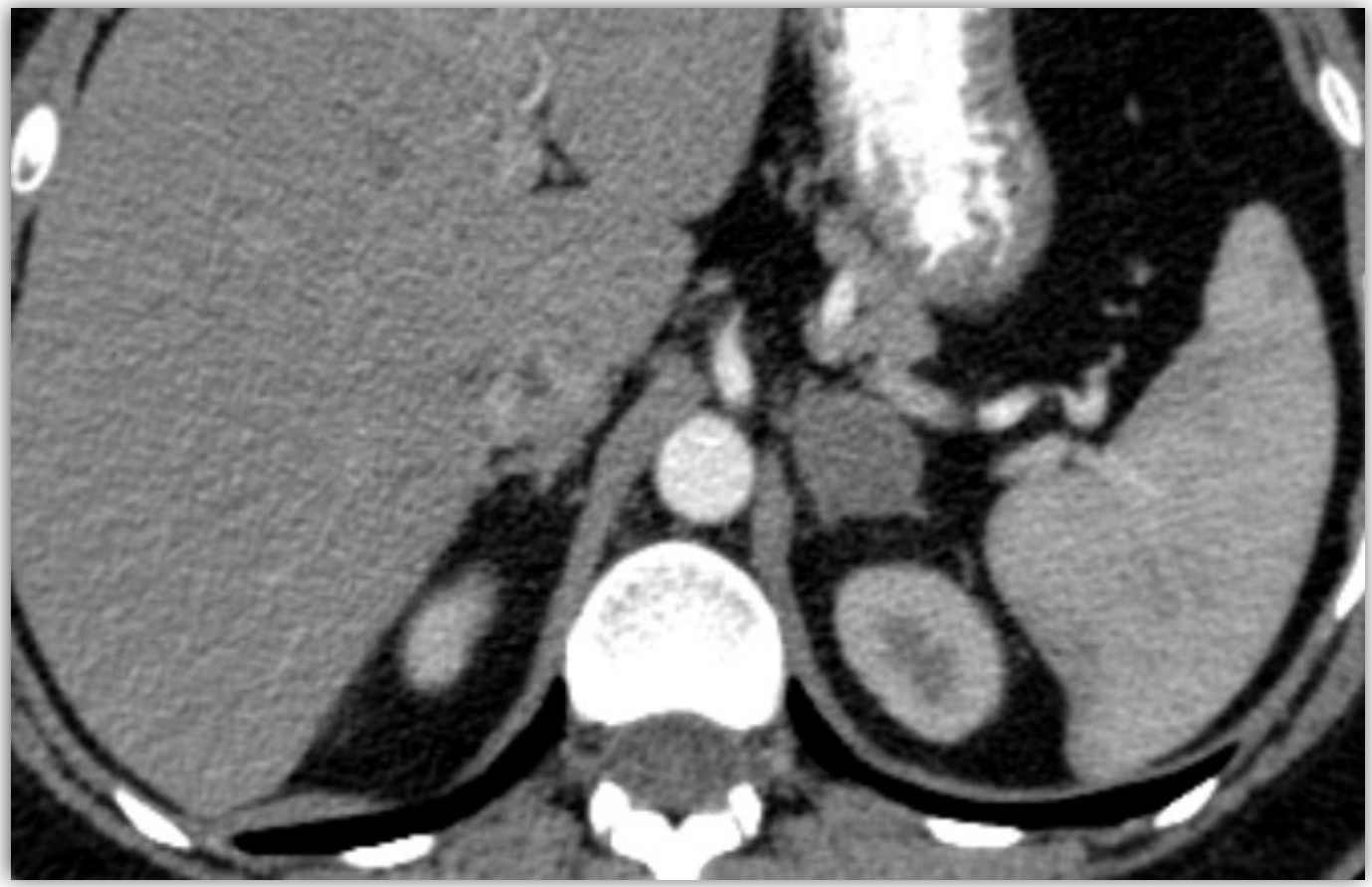
Micronodular Hyperplasia



Macronodular Hyperplasia



Case 1: CT Scan 10/2013 2.3 cm



Case 1 continued

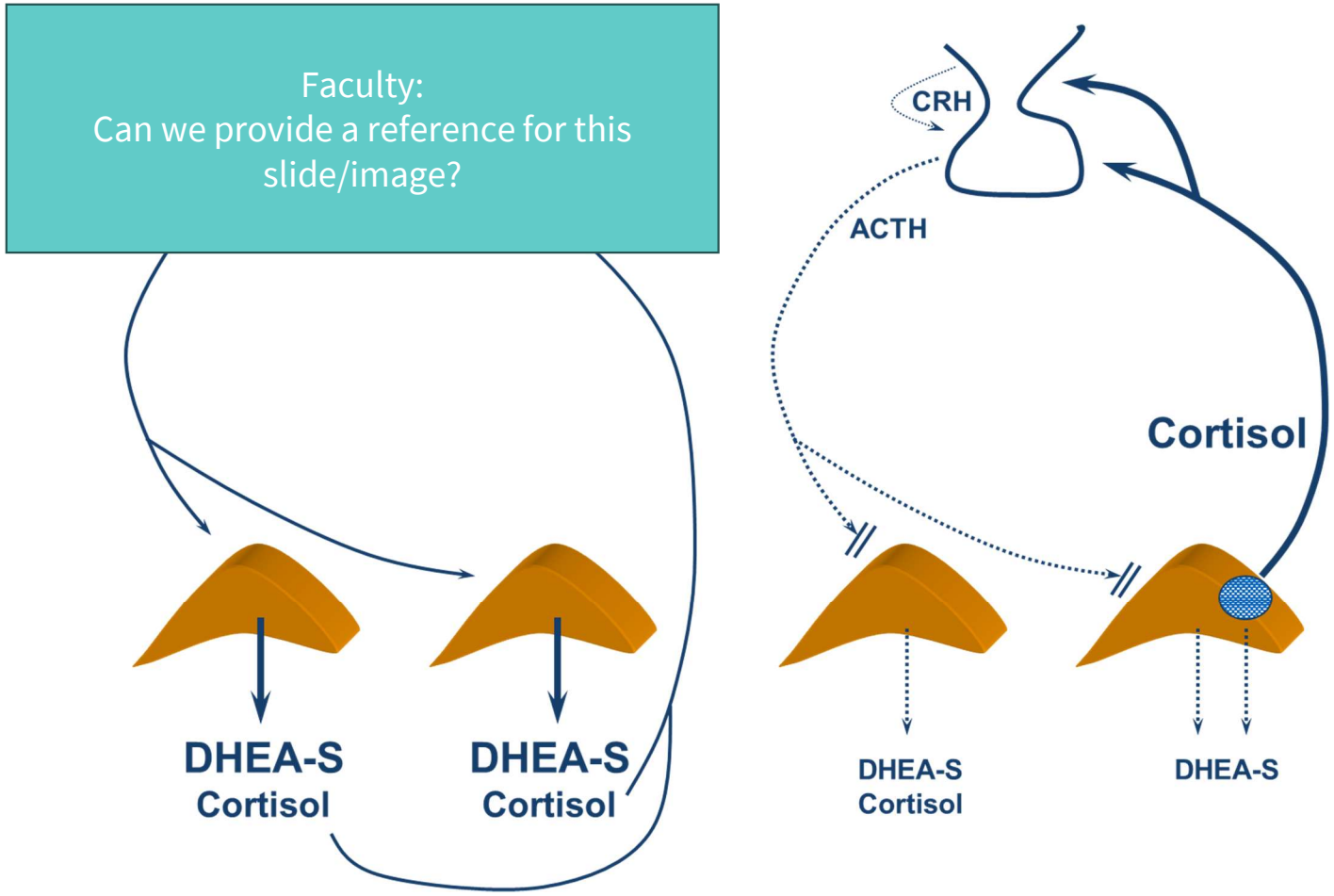
- Initial Laboratory Testing
- ONDST Cortisol 1.4 µg/dL
- Plasma ACTH 14 pg/mL
- Serum DHEAS 126 µg/dL
- Interpretation? Follow-up?

- **Not Strictly Normal But Not Diagnostic**
- **Repeat CT 1 Year**
- **If Stable No Further Testing or FU**

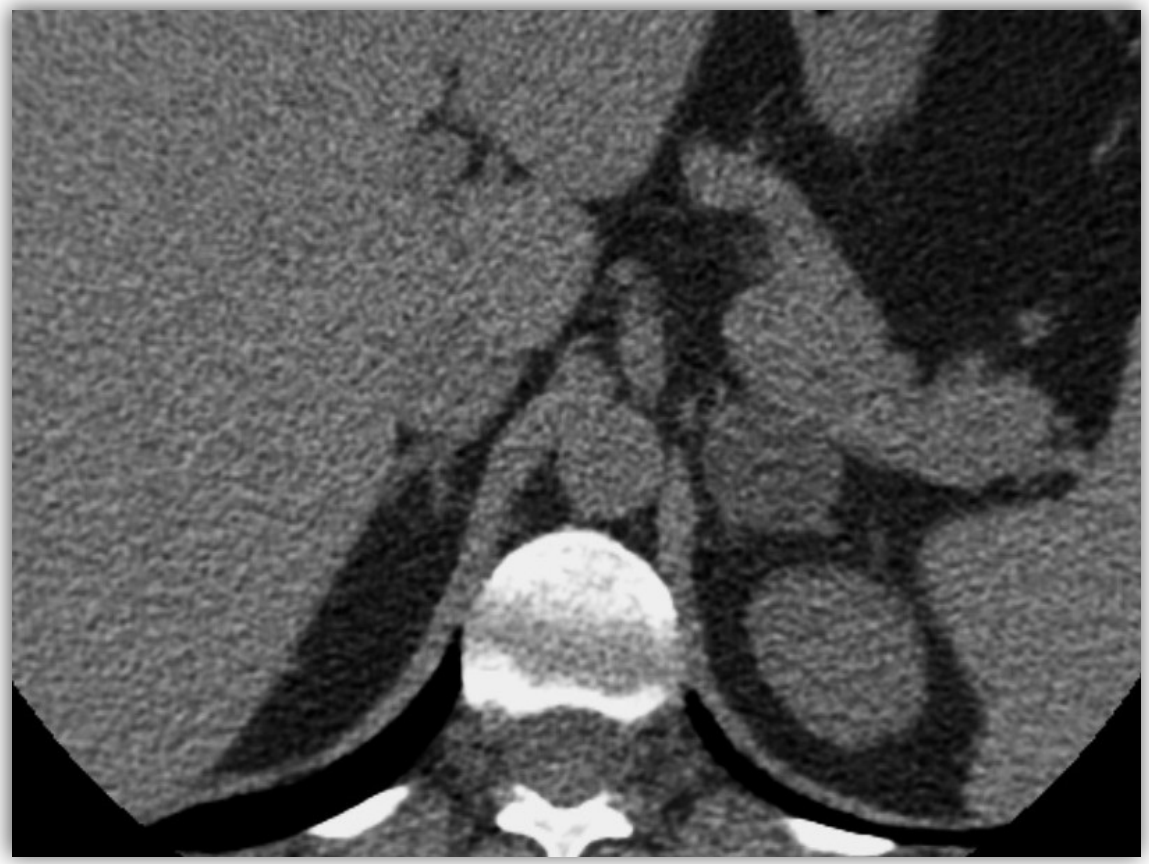
Adrenal Cortex Tumors
Hypercortisolemia Testing

- Overnight 1 mg DST
  - Or 2-3 mg – Suppress ACTH Completely
- Plasma ACTH
  - Must Be Done By 0830, Low Stress
- Serum DHEAS
  - Useful in Patients <65 YO
  - Corroborates Low ACTH
- Repeat Equivocal Labs In 6-12 Weeks

Faculty:
Can we provide a reference for this slide/image?



Case 1: CT Scan 11/2014 2.9 cm



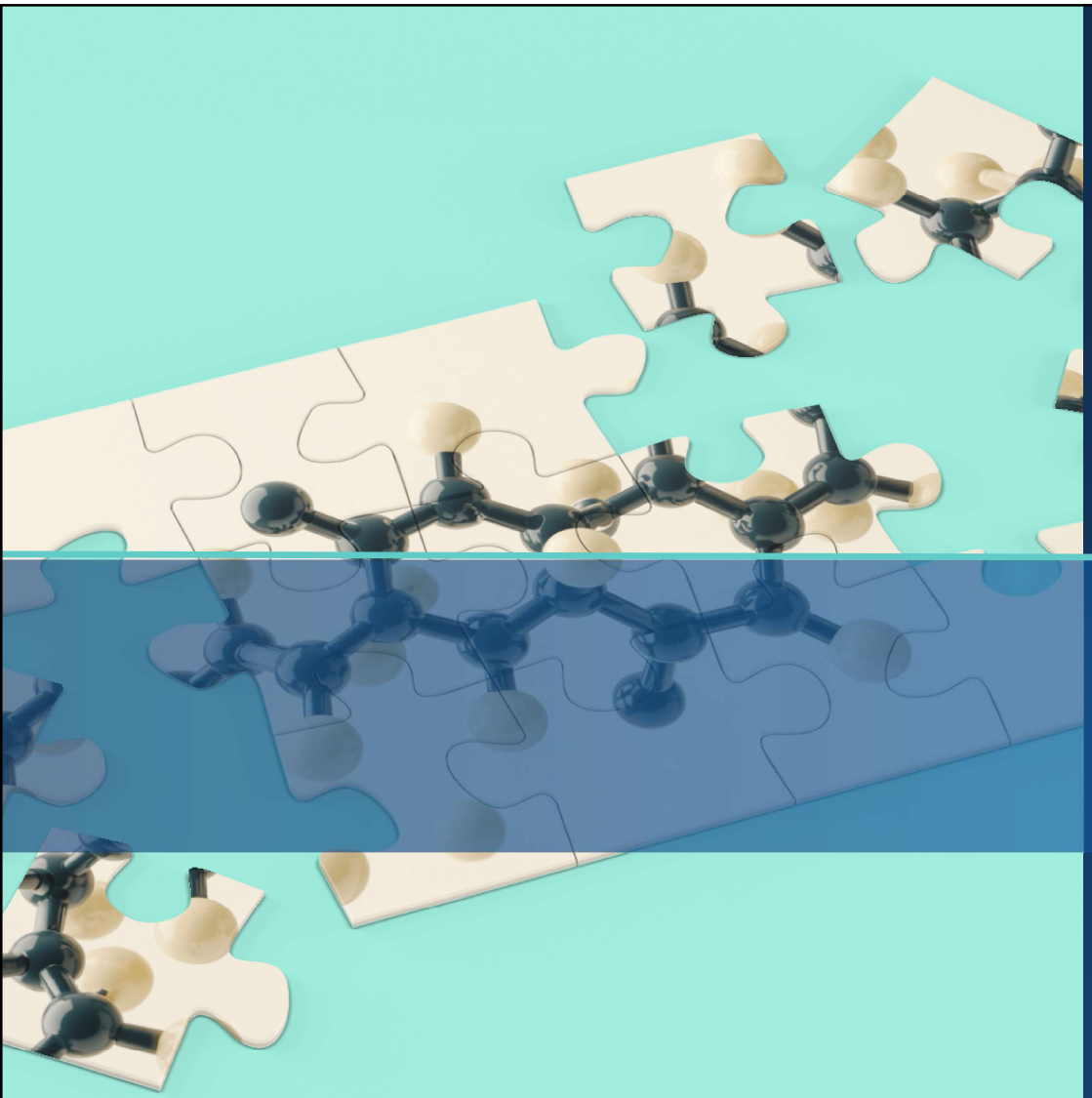
Case 1 – FU Testing

	10/2013	5/2014	10/2014
ACTH (pg/ML)	14	8	2
DHEAS (µg/dL)	126	71	41
ONDST (µg/dL)	1.4	2.1	2.1

Summary: Treatment & Outcome

- Laparoscopic Left Adrenalectomy
  - Resolution of HTN, Normalization of Glucose
  - Physical Findings & Weight Returned to Normal
- But What if She Could Not Have Surgery?
  - Mifepristone For Glucose + Spironolactone for HTN
  - Osilodrostat or Levoketoconazole Carefully Titrate
  - Clinical Trial or Off-Label Treatments
  - Conventional BP & DM Meds Achieve Worse Outcomes

Expert Opinion.



Case 2

60yr old male with abdominal pain

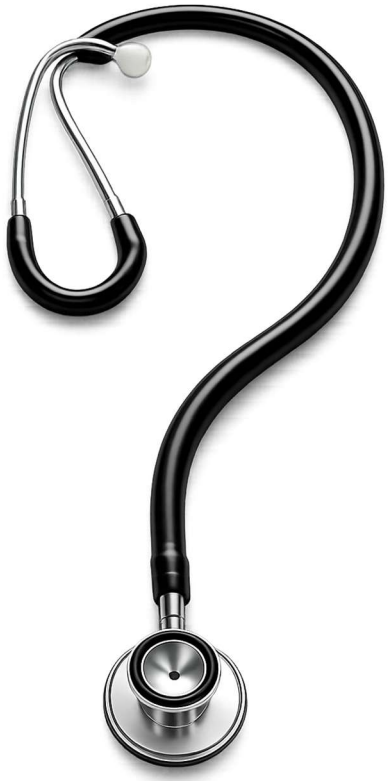
Case 2 Presentation

- 60 years old male patient referred for the incidental finding of bilateral adrenal nodular hyperplasia at CT scan performed for abdominal pain
- Familiar medical history: no hypertension, no diabetes, no endocrinopathies
- Physiologic history: normal physical development; normal gastro-intestinal functions
- Previous medical history: hypertension (onset at 40 yrs); type 2 diabetes detected at age 40. Over the past 6 months, rapid weight gain (10 kg), mild depression mood and erectile disfunction have developed.

Case 2 Presentation (Cont)

- Current therapy: metformin 1 gr BID, valsartan (160 mg/day), amlodipine 10 mg/day, doxazosin 4 mg/day, paroxetine 10 mg/day
- Examination findings: height 175 cm, weight 78 kg, BMI 25.4, BP 135/85,
- Symptoms and physical evaluation: myalgias, weakness, poor libido
- Early laboratory results: mild leucocytosis 12000/µL, glucose 155 mg/dL, HbA1C 7.5%, electrolyte normal, creatinine 0.9 mg/dL, normal thyroid function and calcium-phosphate metabolism

Approach to this Patient (at the 1° visit)

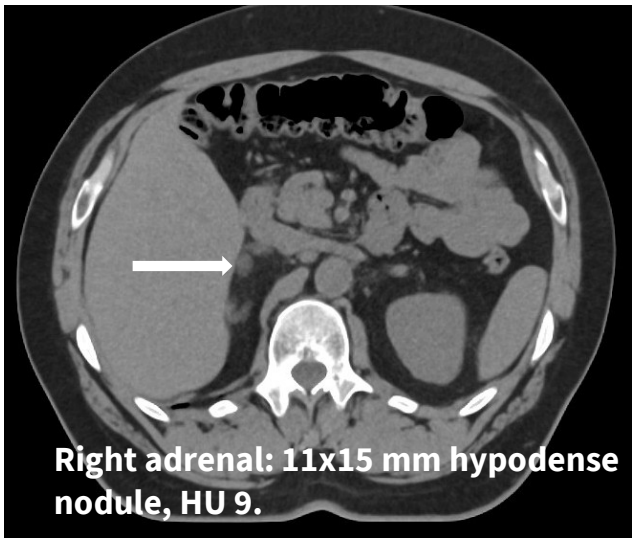


Do you think that this patient should be screened for hypercortisolism and, if yes, **why?**

Diagnosis (2 months after 1° visit)

Endocrine Assessment

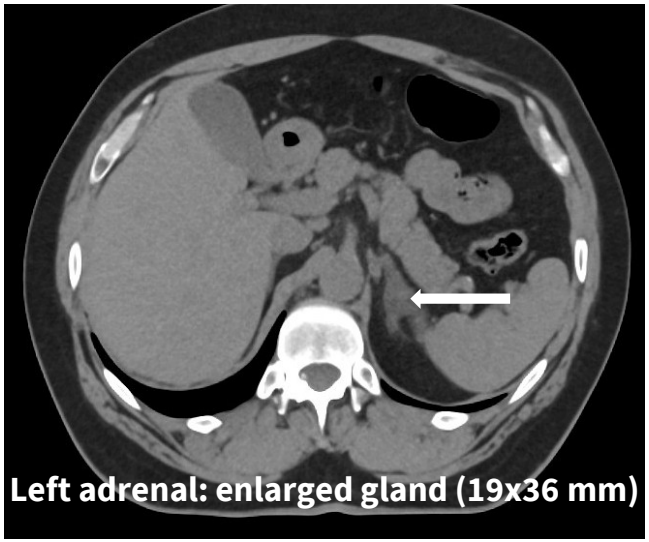
- F-1mgDST: 2.1 µg/dL (vn <1.8)
- LNSalC: 1.97 µg/L (<2.08)
- UFC: 115 µg/24h (nv 15-120)
- Testosterone: 290 ng/dL (nv 300-700)



Right adrenal: 11x15 mm hypodense nodule, HU 9.

Endocrine Assessment

- ACTH 15-16-16 pg/mL (nv 5-55)
- DHEAS 3300 ng/L (nv 650-4700)
- FG: 115 mg/dL (nv 70-110)
- HbA1C: 6.4%



Left adrenal: enlarged gland (19x36 mm)

What diagnosis?

- Non functioning nodular adrenal hyperplasia
- ACTH independent hypercortisolism
- ACTH dependent hypercortisolism

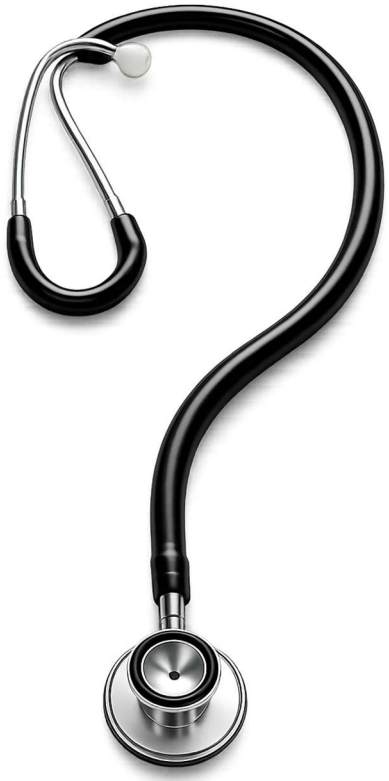
Management

The patient was initially diagnosed as affected by

“ACTH independent hypercortisolism associated with hypertension and type 2 diabetes”.

The patient underwent right adrenal surgery by robot assisted laparoscopy

Are the diagnosis and diagnostic work-up correct?



- Do you think that the diagnosis is correct?
- Are there other comorbidities that should have been studied?

Diagnosis: Comorbidities

- Spinal x-ray: L1 morphometric vertebral fracture (30%) II Grade
- Bone mineral density by Dual X ray Absorptiometry
    - Lumbar spine (L2-L4) T-score L2-L4 -2.6 (Z-score -2.2)
    - Femoral neck T-score -1.8 (Z-score -1.5)
    - Total Hip T-score -1.9 (Z-score -1.6)
- 24h BP monitoring: diurnal adequate control (diurnal BP 132/82 mmHg), but loss of circadian rhythm (nocturnal BP 125/82)

Follow up (4 months after adrenal surgery)

No secondary hypocortisolism

Clinical features:

- Persistence of symptoms
- Stable blood pressure
- Maintenance of full anti-hypertensive therapy
- Stable glucometabolic control
- Stable weight (64 kg)
- Persistence of depressed mood
- Persistence of erectile dysfunction

Endocrine assessment:

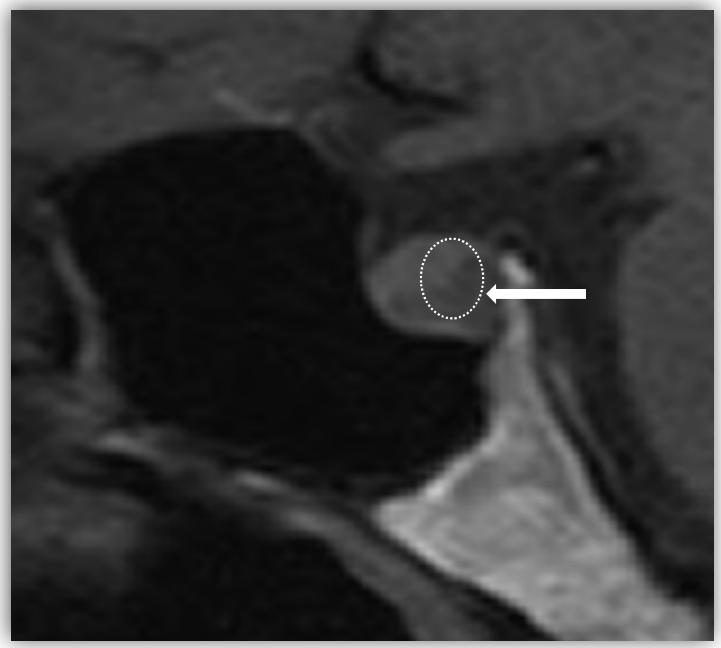
- Morning Cortisol: 19 µg/dL (nv 5-20)
- ACTH 49 pg/mL (nv 5-55)
- LNSalC: 2.1 µg/L (<2.08)
- F-1mgDST: 2.5 µg/dL (vn <1.8)
- UFC: 110 µg/24h (nv 15-120)
- DHEAS 4300 ng/L (nv 650-4700)
- Testosterone: 270 ng/dL (nv 300-700)
- FG: 136 mg/dL (nv 70-110)
- HbA1C: 8.5%

What diagnosis? (more than 1 is possible)

- Non functioning adrenal hyperplasia
- Persistent ACTH independent hypercortisolism
- ACTH-dependent hypercortisolism

Diagnosis: ACTH dependent hypercortisolism (8 months after adrenal surgery)

- ACTH 55-45 pg/mL (nv 5-55)
- F-1mgDST: 3.5 µg/dL (vn <1.8)
- CRH-test: ACTH 55→ 160 pg/mL (>100%)
- F-8mgDST: cortisol 22 → 5 µg/dL (>50%)
- LNSC 5.3 µg/dL (nv <4.0)
- UFC: 130 µg/24h (nv 15-120)
- FG: 140 mg/dL (nv 70-110)
- HbA1C: 9.5



MRI: 8 mm iso-to hyperintense on T2-weighted images pituitary lesion

Follow-up (6 months after pituitary surgery)

- The patient was diagnosed with *"ACTH-dependent hypercortisolism of pituitary origin"* and underwent pituitary surgery.
- Secondary hypocortisolism occurred
- She was initiated with cortisone acetate 25 mg/day (3 fractionated daily doses)

Clinical features

- Hypocortisolism
- Controlled BP and normal BP circadian rhythm
- Reduction of anti-hypertensive therapy to only amlodipine 5 mg/day
- Normalized FG levels and metformin withdrawn
- 4 kg weight loss
- Disappearance of depressed mood
- Amelioration of libido and erectile dysfunction
- Disappearance of hypogonadism

Endocrine assessment

- Morning cortisol 2 µg/dL
- ACTH 20 pg/mL (nv 5-55)
- F-1mgDST: 0.5 µg/dL (vn <1.8)
- UFC: 18 µg/24h (nv 15-120)
- 75-OGTT: Glucose 86-102 mg/dL
- HbA1C: 5.9%
- Testosterone: 490 ng/dL (nv 300-700)

Summary

- In a patient with unexplainable hypertension and/or altered glucose metabolism the presence of hypercortisolism should be investigated
- The presence of an adrenal nodule in the context of hypercortisolism should not be considered definitive proof of ACTH independence
- In patients with hypercortisolism the presence of asymptomatic vertebral fracture, altered BP circadian rhythm, glucose intolerance and/or diabetes should be investigated.

Interprofessional Team Overview: What is the Role(s) of the Care Team?

Physicians: Endocrinologists work with primary care, internists, neurosurgeons, endocrine surgeons, radiologists, pathologists

- Screen, diagnose, determine and oversee treatment plans

Advanced Practice Providers: Nurse Practitioners, Physician Assistants

- Perform patient assessments, manage symptoms, provide follow-up care, and support treatment delivery in collaboration with physicians

Clinical Pharmacy Specialists:

- Optimize pharmacologic treatment plans, educate patients on medication use and side effects, and answer drug information questions

Nurses:

- Provide day-to-day care coordination, triage symptoms, administer treatments, and serve as key points of patient contact
- Educate patients and families about care plans and procedures

Social Workers:

- Address psychosocial needs, coordinate resources (transportation, financial support, counseling), and facilitate communication between patients, families, and the care team

Clinical Takeaways

- In patients with unilateral cortisol secreting adenoma and hypercortisolism, laparoscopic adrenalectomy is the treatment of choice
- Laparoscopic adrenalectomy leads to amelioration of HTN and amelioration/normalization of glucometabolic control
- The presence of an adrenal nodule in the context of hypercortisolism should not be considered definitive proof of ACTH independence
- In patients with hypercortisolism the presence of asymptomatic vertebral fracture, altered BP circadian rhythm, glucose intolerance and/or diabetes should be investigated

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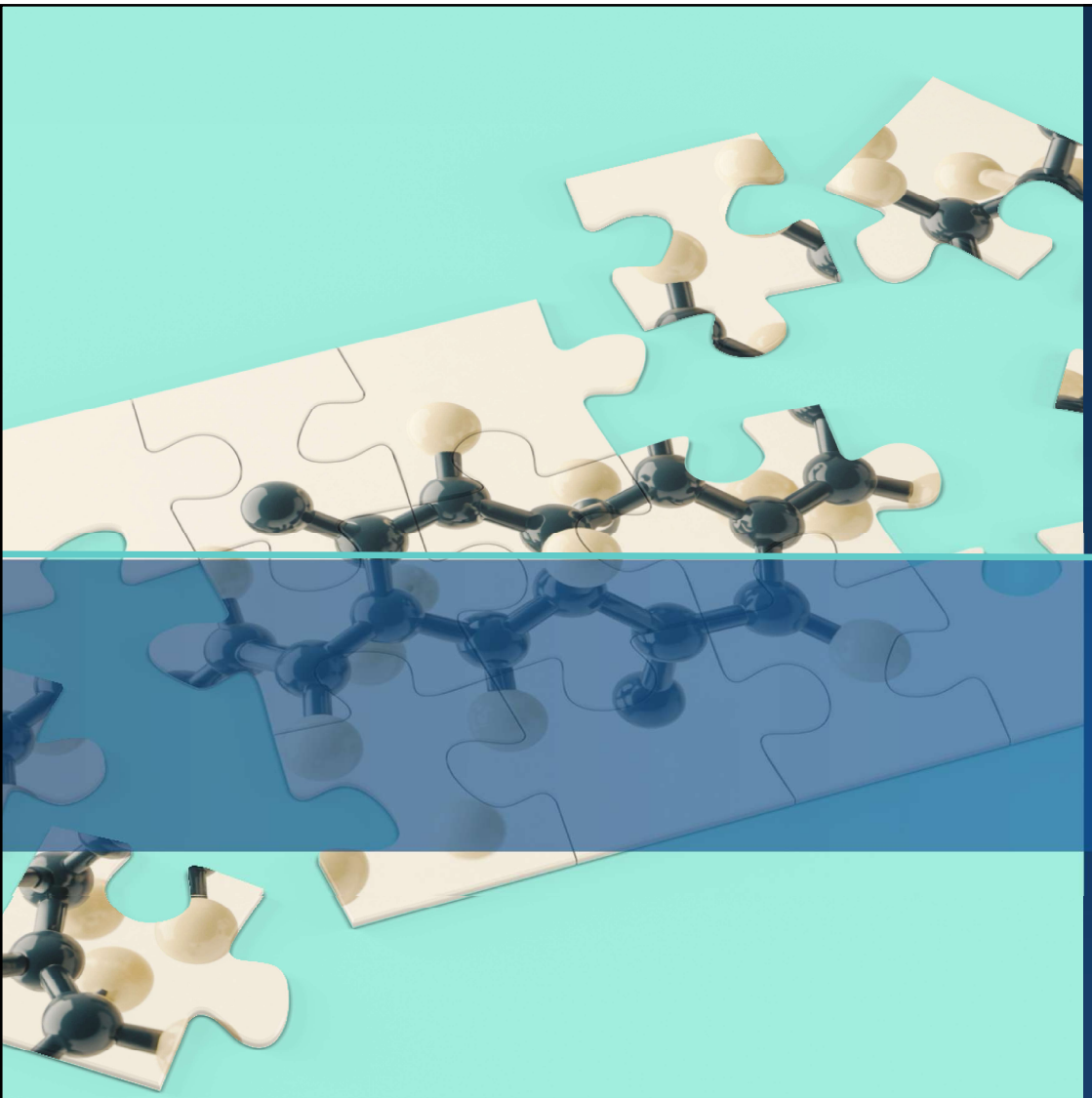

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