The Case of the Adrenal Mass
Functional Adrenal Tumors

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10.2.14
Kings County Hospital

www.downstatesurgery.org
Case presentation

• 62 year old F
• PMH: HTN, DM, arthritis
• PSH: none
• Meds: Metoprolol, Nifedipine, Losartan, Chlorthalidone, ASA, Metformin, Glipizide
• NKDA
• No EtOH/drug/tobacco use
• July 2012 c/o palpitations
• **VS:** BP 152/60  HR 116 RR 16  Afebrile
• **Exam:**
  - Gen: obese, nad, A+Ox3
  - CV: tachycardic, regular rhythm
  - Skin: multiple hyperpigmented macules, no striae, bruising, or abnormal hair growth
  - Abd: obese, soft, nontender to palpation
• **EKG**: sinus tachycardia, LVH

• **Labs**: Na 139  K 3.1  BUN/Cr 29/1.36  
  Gluc 175  
  Albumin 4.4  
  TSH 0.6  T4 1.06  
  Troponin negative x3

• **Imaging:**
  - **ECHO** – EF 50-55%, LVH
  - **CTA C/A/P**
# Lab workup

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone</td>
<td>5</td>
<td>&lt;28 (ng/dL)</td>
</tr>
<tr>
<td>Renin</td>
<td>0.61</td>
<td>0.25-5.82 (ng/ml/h)</td>
</tr>
<tr>
<td>ACTH</td>
<td>6</td>
<td>6-50 (pg/mL)</td>
</tr>
<tr>
<td>Urine catecholamine</td>
<td>WNL</td>
<td></td>
</tr>
<tr>
<td>Serum cortisol</td>
<td>25.35</td>
<td>4.3-22.4 (ug/dL)</td>
</tr>
<tr>
<td>Urine cortisol</td>
<td>595.2</td>
<td>28.5-213.7 (ug/24hr)</td>
</tr>
<tr>
<td>Dexamethasone suppression test</td>
<td>1.48</td>
<td>0.07-0.93 (mcg/dL)</td>
</tr>
</tbody>
</table>
Surgery clinic appointments

- July 2013
- October 2013
- February 2014
- March 2014
- May 2014 – scheduled for surgery – cancelled by patient for personal reasons
9/2/14

- Laparoscopic left adrenalectomy
- Post-operative steroid taper
- Discharged home POD#3
- Pathology: adenoma
Introduction

- **1563** – Eustachius first anatomic account
- **1805** – Cuvier described anatomic division of cortex and medulla
- **1855** – Addison described adrenal insufficiency
- **1885** – Frankel identified pheochromocytoma
- **1897** – Adrenaline identified as agent of adrenal medulla elevating BP in dogs
- **1932** – Cushing described 11 patients with moon facies, truncal obesity, hypertension
- **1952** – Aldosterone identified by Conn
Anatomy

**Arterial** – 3 sources

1. Inferior phrenic
2. Renal artery
3. Aorta

**Venous**
- Right – IVC
- Left – renal vein
Pop quiz!

- **Arterial** – 3 sources
  1. Inferior phrenic
  2. Renal artery
  3. Aorta

- **Venous**
  - Right – IVC
  - Left – renal vein
Anatomy

Transverse section

Capsule

Zona glomerulosa
Mineralocorticoids: Aldosterone

Zona fasciculata
Glucocorticoids: Cortisol

Zona reticularis
Sex steroids: Progesterone, androgens, estrogen precursors

MEDULLA
Catecholamines

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Aldosterone

- Major adrenal mineralocorticoid
- Regulated by the renin-angiotensin system
- Decreased renal blood flow, decreased plasma sodium, increased sympathetic tone → renin release
- Function – increase Na reabsorption and K and H+ excretion at renal distal convoluted tubule
Cortisol

- Major adrenal glucocorticoid
- Hypothalamic-pituitary-adrenal axis
- Diurnal variation

**Table 38-18 Features of Cushing’s Syndrome**

<table>
<thead>
<tr>
<th>System</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Weight gain—central obesity, buffalo hump, supraclavicular fat pads</td>
</tr>
<tr>
<td>Integumentary</td>
<td>Hirsutism, plethora, purple striae, acne, ecchymosis</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Generalized weakness, osteopenia</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>Emotional lability, psychosis, depression</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Diabetes or glucose intolerance, hyperlipidemia</td>
</tr>
<tr>
<td>Renal</td>
<td>Polyuria, renal stones</td>
</tr>
<tr>
<td>Gonadal</td>
<td>Impotence, decreased libido, menstrual irregularities</td>
</tr>
</tbody>
</table>
Androgens

• DHEA, DHEAS

• Peripheral conversion to testosterone and dihydrotestosterone

• Fetal development – male genitalia

• Development of secondary sexual characteristics at puberty

• Androgen excess
  o Boys - precocious puberty in boys
  o Girls - acne, and hirsutism, anovulation
Catecholamines

- Norepinephrine, epinephrine, dopamine – Adrenal medulla
- Synthesis from Tyrosine
- N-methyltransferase present in adrenal glands
- Metabolism to metanephrines, normetanephrines, VMA
Functional Adrenal Tumors
Benign

- Cortisol-producing (Cushing’s syndrome)
- Aldosteronoma (Conn’s syndrome)
- Sex-steroid-producing
- Pheochromocytoma

Malignant

- Adrenal cortical carcinoma
- Malignant pheochromocytoma
- Metastatic disease to adrenal gland
Benign
Cortisol-producing Adenoma

- **Cushing’s syndrome** – complex of symptoms related to hypersecretion of cortisol regardless of etiology
- **Cushing’s disease** – pituitary tumor

### Table 38-17 Etiology of Cushing’s Syndrome

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH-dependent (70%)</td>
<td></td>
</tr>
<tr>
<td>Pituitary adenoma or Cushing’s disease (~70%)</td>
<td></td>
</tr>
<tr>
<td>Ectopic ACTH production (~10%)</td>
<td></td>
</tr>
<tr>
<td>Ectopic CRH production (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>ACTH-independent (20–30%)</td>
<td></td>
</tr>
<tr>
<td>Adrenal adenoma (10–15%)</td>
<td></td>
</tr>
<tr>
<td>Adrenal carcinoma (5–10%)</td>
<td></td>
</tr>
<tr>
<td>Adrenal hyperplasia—pigmented micronodular cortical hyperplasia or gastrin inhibitory peptide-sensitive macronodular hyperplasia (5%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Pseudo-Cushing’s syndrome</td>
<td></td>
</tr>
<tr>
<td>Iatrogenic—exogenous administration of steroids</td>
<td></td>
</tr>
</tbody>
</table>
Cortisol-producing adenoma: H+P

- Hypertension, diabetes, osteopenia
- **ROS**: Generalized weakness, headaches, weight gain, depression, emotional lability, decreased libido, menstrual irregularities
- **Exam**: Central obesity, moon facies, buffalo hump, supraclavicular fat pads, purple striae, acne
Cortisol-producing adenoma: Laboratory studies

- Elevated 24 hour urinary cortisol level OR
- Low-dose dexamethasone suppression test

- Plasma ACTH levels
  - Suppressed → Primary cortisol-secreting adrenal tumors
  - Elevated → Adrenal hyperplasia due to pituitary tumor and CRH-secreting tumors; highest in those with ectopic ACTH producing tumors

- High-dose dexamethasone suppression test
  - Failure to suppress urinary cortisol by 50% → Ectopic
  - Suppression: pituitary tumor
Cortisol-producing adenoma: Imaging

**CT**
- Hounsfield unit (HU) <10
- Percentage washout - HIGH

**MRI**
- Better assessment vascular anatomy
Cortisol-producing adenoma: Treatment

- Laparoscopic adrenalectomy
- Pre and post-operative steroids
- Duration of treatment – ACTH stimulation test
Aldosteronoma (Conn’s syndrome)

- Hyperaldosteronism – renal artery stenosis, CHF, cirrhosis, b/l adrenal hyperplasia
- Primary hyperaldosteronism – autonomous aldosterone secretion → suppression of renin secretion
- 30-50 years
- 1% hypertension
- Associated with hypokalemia
Aldosteronoma (Conn’s syndrome)

H+P

- Hypertension
- Difficult control – multiple drug Rx
- ROS: weakness, fatigue, headaches, polydipsia/polyuria, muscle weakness
Aldosteronoma (Conn’s syndrome)

Laboratory studies

- Na, K
- Hypokalemia on diuretic therapy
- Aldosterone:renin ratio
  - >30 suspect
- Sodium loading test
  - No suppression

*Including spironolactone, ACE inhibitors, diuretics, β-blockers.*
Aldosteronoma (Conn’s syndrome)
Localization/Imaging

- CT/MRI
- Equivocal: Adrenal vein sampling
  - Lateralization: aldosteronoma
  - Non-lateralization: bilateral adrenal hyperplasia
- NP 59 study
Aldosteronoma (Conn’s syndrome)

Treatment

- Aldosteronoma
  - Pre-op – HTN control, correction of K
  - laparoscopic adrenalectomy or posterior open approach unless carcinoma suspected → anterior abdominal approach
  - Post-op – mineralocorticoid for up to 3 months

- Bilateral adrenal hyperplasia – medical management - spironolactone
Sex-steroid producing adenoma

- **Women** – hirsutism, amenorrhea, infertility, increased muscle mass, deepened voice, temporal balding
- **Men** – present in advanced stages
- **Children** – accelerated growth, premature development of facial and pubic hair, acne, genital enlargement, deepening of voice

- **Feminizing tumors** – least common
  - **Men** – gynecomastia, impotence, testicular atrophy
  - **Women** – irregular menses or dysfunctional uterine bleeding
  - **Girls** – precocious puberty, early menarche
Sex-steroid producing adenoma

Labs/Treatment

- Androgen precursor DHEA
- Measure 17-ketosteroids
- Adrenalectomy
- Metastatic disease – adrenolytic drugs
  - Mitotane
  - Ketoconazole
Pheochromocytoma

• Chromaffin cells
• Rare, 0.3-0.95%
• Male=Female
• Rule of 10s:
  ➢ 10% bilateral
  ➢ 10% malignant
  ➢ 10% pediatric patients
  ➢ 10% extra-adrenal
  ➢ 10% familial (MEN2a, MEN2b, VHL)
• Found in 0.1-0.2% of hypertensive patients
• Extra-adrenal – 3x more malignant
Pheochromocytoma
H+P

• Headaches, palpitations, diaphoresis – Classic triad
• Anxiety, tremulousness, chest pain, SOB, nausea/vomiting
• Hypertension – most common
• Sudden death in patients with undiagnosed tumors undergoing biopsy or other surgeries
Pheochromocytoma Labs
Pheochromocytoma Imaging

- **CT** 85-95% sensitive
- Should include diaphragm to aortic bifurcation
- **MRI** – more sensitive and specific

- Metaiodobenzylguanidine (MIBG) -
Pheochromocytoma Management

**PREOP**
1. Alpha-blockade – Phenoxybenzamine
   - Start 1-3 weeks prior to surgery (10 mg BID)
   - Volume repletion
2. Beta-blockade – Propanolol
   - 10-40 mg q6-8 H
   - Must administer after alpha-blockade!

**SURGERY**
- Laparoscopic adrenalectomy <5cm, o/w open
- Minimal tumor manipulation/capsule rupture
- Induction
- Intraoperative BP control
- Post-op volume repletion
Malignant
Adrenocortical carcinoma

- Incidence 2 in 1 million
- Bimodal age distribution
- Majority sporadic, some association with germline mutations
- Large tumors (>6cm) at time of Dx
- Hypersecretory or mixed
- 50% non-functioning
- 0-25% of incidentalomas
- Poor prognosis (median survival 18 months)

- 35% Mixed
- 30% cortisol
- 20% androgens
- 10% estrogens
- 2% aldosterone
Adrenocortical carcinoma
H+P

• Functioning tumors often present with Cushing’s syndrome + virilizing features

• Non-functioning
  ➢ Enlarging abdominal mass
  ➢ Abdominal or back pain
  ➢ Weight loss, anorexia, nausea
Adrenocortical carcinoma

Labs/Imaging

- CT/MRI
- Size *** >6cm
- Tumor heterogeneity, irregular margins, presence of hemorrhage, adjacent lymphadenopathy, liver metastases

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Adrenocortical carcinoma

Treatment

• Most important predictor of survival – adequacy of resection

• Complete resection – 32-48% 5 year survival

• Incomplete excision – median survival <1 year
Adrenal metastases

- Common site of metastasis
- Breast, lung, GI tract, melanoma, kidney
- Autopsy review, metastases found in 27% of 1,000 patients
- Most asymptomatic, incidental finding
- Imaging – delayed contrast washout
- FNA after r/o pheochromocytoma
- Surgical resection if solitary
- Improved survival 31 months vs. 8.5 months
Adrenal Incidentaloma

- Definition
- 0.4-4.4% incidence on CT
- Autopsies: 1.4-9%
Size does matter?

- Risk of malignancy
  - <2% in <4 cm
  - 6% 4-6 cm
  - >25% in >6 cm

A: Data from eight studies with histologically determined diagnoses (n = 103) relating to tumor size.
Adrenal Incidentalomas

2 questions:
- Is it functional
- Is it malignant

→ surgery
Question 1

- A 45 year old woman with a hx of HTN undergoes CT A/P after presenting to the ER with RLQ pain. The study is negative except for an incidentally found 3 cm mass in the R adrenal. Evaluation reveals elevated urine metanephrines. Based on this result the lesion is most likely located in the:

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B. Zona fasciculate
C. Zona reticularis
D. Medulla
E. Para-adrenal tissues
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Question 2

- A 47 year old female has recent onset headaches, palpitations, sweating and heat intolerance. On PE her BP 190/100 and her HR 110. Biochemical evaluation revealed an elevated plasma metanephrine level and elevated 24 hr urinary metanephrine level. A CT A/P demonstrates 3 cm left adrenal mass. Which of the following should be the next most appropriate step?

A. MIBG scan
B. Somatostatin scintigraphy
C. MRI
D. PET
E. No further imaging needed
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A 51 year old female reports significant weight gain over the past 6 months. In this period she had 2 episodes of UTI and noticed that she bruised more easily. On PE her BP 150/95. She is 68 inches tall and weighs 250 lbs. She has a characteristic bulge of fat on her back and striae on her abdomen. Which of the following statements about the disease is TRUE?

A. Ectopic ACTH secretion is most often caused by medullary thyroid cancer
B. Cushing disease is the most common cause of endogenous Cushing’s syndrome
C. An elevated spot urinary free cortisol is diagnostic for Cushing’s syndrome
D. Cushing’s syndrome can be excluded by measuring a C-peptide level
E. An adrenal adenoma causes ACTH-dependent Cushing’s syndrome
Question 3

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References

- **Brian J. Gallay, MD PhD**, **Suhail Ahmad, MD**, **Lei Xu, PhD**, **Bert Toivola, PhD**, **Robert C. Davidson, MD**, **Screening for primary aldosteronism without discontinuing hypertensive medications: Plasma aldosterone-renin ratio** *American Journal of Kidney Diseases*, Volume 37, Issue 4, April 2001, Pages 699–705


- William F. Young* and Anthony W. Stanson†, What are the keys to successful adrenal venous sampling (AVS) in patients with primary aldosteronism? *Clinical Endocrinology* (2009) 70, 14–17

- Paul R. Gittens Jr., Surgical management of metastatic disease to the adrenal gland Jefferson Digital Commons April 2008

- Schwartz Chapter 38: Thyroid, Parathyroid, and Adrenal

- Terzolo, M; Subclinical Cushing’s syndrome: Definition and Management; *Clinical Endocrinology*, 2012 76:12-18


- Williams Textbook of Endocrinology: Adrenal adenomas, incidentalomas, and carcinomas