Case Presentation

Gordon Callender, MD
Department of Surgery
PGY-4
• **Chief Complaint**: Abdominal pain

• **History of Present Illness**: 43 y.o. black female with multiple medical problems presented to the ER 7 years prior with vague left sided abdominal pain. Denied any changes in weight, appetite, bowel habits, -N/-V. The patient was noted to have poorly controlled BP on multiple meds.
History

- **PMHx**: HTN, asthma, obesity, sickle cell trait, CHF.
- **PSHx**: Denies
- **All**: NKDA
- **SHx**: Non-contributory
- **Meds**: Norvasc, labetalol, spironolactone, lasix, claritin, MVI
• CT Scan in 1997 revealed a left adrenal mass; the patient’s hypokalemia, and serum aldosterone levels were c/w Conn’s syndrome.

• Patient initially refused to undergo any surgical intervention and was managed medically.

• Patient was lost to follow up with the surgical service until 2004 when she c/o of worsening BP control and agreed to have a resection.
Physical Exam & Labs

Vitals: BP 143/78 P 79 R 20 Afebrile BMI: 41.3 kg/m² (Wt: 112 kg, Ht: 165 cm)

General: A&O x3, NAD, anicteric

Chest: CTA B/L

Cor: S1S2, RRR

Abdomen: Soft, Obese, ND/NG/NT, no palpable masses.

Aldosterone: 35 (2-9 ng/dl)
Urine Preg: neg
U/A: neg
Radiology

- **CXR**: No Active Pulmonary Disease
- **CT Scan of Abdomen/Pelvis**: Left adrenal adenoma measuring 2 cm in greatest dimension.
Operative Course

• **Approach:**
  - Transperitoneal laparoscopic left adrenalectomy

• **Findings:**
  - 2 cm left adrenal gland

• **Intervention:**
  - Resection of tumor using harmonic scalpel
Pathology

Specimen

H&E Microscopy
Post-Operative Course

- **POD #0**: Tolerated clear liquid diet.
- **POD #1**: Advanced to regular diet and discharged normotensive only on Norvasc 10 mg QD.
- K+ normalized when the patient f/u in clinic without supplements, and patient’s BP remained normotensive.
Workup & Management of Functional Adrenal Tumors
Discussion Topics

History
Embryology
Anatomy & Physiology
Steroid Biochemistry
Adrenal Tumors
  • Signs & Symptoms
  • Types
    • Incidentalomas
    • Functional Tumors
Indications for Adrenalectomy
  • Laparoscopic Adrenalectomy
  • Video
History

- Cushing described excess cortisol elaboration in 1912.
- Conn described hyperaldosteronism in 1955.
- Congenital adrenal hyperplasia was reported in 1865 but not fully elucidated until 1939.
- Frankel described pheochromocytomas in 1886.
Embryology

- Consists of two functionally distinct endocrine glands:
  - The cortex arises from coelomic mesoderm adjacent to the urogenital ridge between the 4th and 6th gestational weeks. Contains the *zona glomerulosa*, *zona fasiculata* & *zona reticularis*.
  - The *medulla* develops with the sympathetic nervous system. During the 5th week of gestation, neural crest cells migrate to the para-aortic region to the medial aspect of the adrenal cortex.
Anatomy & Physiology

- Bilateral retroperitoneal organs found just superior to the upper pole of each kidney.
- Weigh approximately 4 gm.
- **Right adrenal**: juxtaped to the inferior vena cava and is next to the right diaphragmatic crus and bare area of the liver.
- **Left adrenal**: located between left kidney and aorta, near tail of pancreas and the splenic artery.
Adrenal Steroid Biochemistry

- **Primary function of adrenal cortex**: production of glucocorticoids, mineralcorticoids, adrenal adrogens.

- **Mineralcorticoids**: synthesized in the zona glomerulosa.

- **Glucocorticoids & Androgens**: synthesized in the zona fasiculata.

- Adrenal steroids all have 19 or 21 C atoms, with a common 17-C skeleton.
# Adrenal Tumors

<table>
<thead>
<tr>
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<td>metastasis</td>
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Signs & Symptoms

- Non-functional adrenal masses are usually asymptomatic unless they present with hemorrhage. Usually are found on workup for another process.

- Functional adrenal masses may present with hypertension, hypokalemia and muscle weakness, or stigmata of Cushing’s or adrogenital syndrome.
Types of Adrenal Tumors
Non-Functioning Adrenal Tumors
Incidentalomas

- Adrenal lesions found on imaging study performed for another indication.
  - Frequency: 1-4%
  - Most (36-94%) are small, non-functioning, benign adenomas
  - Incidence of carcinoma: ~5%. Increases to 10% if > 4 cm, 25-98% if > 6 cm.
  - Most authors agree if imaging findings c/w malignancy (i.e. local invasion, regional lymphadenopathy, or mets): open adrenalectomy.
  - Some recommend resecting lesions > 3 cm in young patients with no comorbidities, and > 5 cm in older patients.

Functional Adrenal Tumors
## Adrenal Causes of Hypertension

### Physiologic Mechanisms in Adrenal Hypertension

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<td>Autonomous hypersecretion of aldosterone (hypermineralocorticoidism)</td>
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4.2 Hypertension and the Kidney

Adrenal Hypertension

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Functional Tumors: Primary Aldosteronism

<table>
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<th>Types</th>
<th>Relative Frequency</th>
</tr>
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<tr>
<td>Solitary adrenal adenoma</td>
<td>65 %</td>
</tr>
<tr>
<td>Bilateral adrenal hyperplasia</td>
<td>30 %</td>
</tr>
<tr>
<td>Unilateral adrenal hyperplasia</td>
<td>2 %</td>
</tr>
<tr>
<td>Glucocorticoid-remediable aldosteronism</td>
<td>&lt; 1 %</td>
</tr>
<tr>
<td>Bilateral solitary adrenal adenomas</td>
<td>&lt; 1 %</td>
</tr>
<tr>
<td>Adrenal carcinoma</td>
<td>&lt; 1 %</td>
</tr>
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Functional Tumors: Primary Aldosteronism

- **Diagnosis:**
  - Previously considered in patients on multiple medications with spontaneous hypokalemia and still hypertensive. Prevalence: <.5% hypertensive patients.
  - Currently recommended to measure serum plasma renin activity & divide by the plasma aldosterone concentration (i.e., PRA / PAC ratio). If the ratio ≥ 20 & PAC ≥ 15 ng/dL then it is highly suggestive of Primary Aldosteronism.
  - 24-Hour Urine Collection may be performed in equivocal cases to document inappropriate K wasting, especially following a high Na diet for provocation (>30 mEq/day with hypokalemia)

<table>
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<tr>
<th>Test</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
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<tr>
<td>Serum potassium ≤ 3.5 mEq/L</td>
<td>75</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Plasma renin activity ≤ 4 ng/mL/90 min</td>
<td>&gt;99</td>
<td>40–60</td>
</tr>
<tr>
<td>Urinary aldosterone ≥ 20 μg/d</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>Plasma aldosterone ≥ 15 ng/dL</td>
<td>90</td>
<td>60</td>
</tr>
<tr>
<td>Plasma aldosterone:plasma renin activity ratio ≥ 15</td>
<td>99.8</td>
<td>98</td>
</tr>
<tr>
<td>Plasma aldosterone:plasma renin activity ratio ≥ 30</td>
<td>96</td>
<td>100</td>
</tr>
</tbody>
</table>

**FIGURE 4-7**

Screening tests for primary aldosteronism. Serum potassium levels range from 3.5 to normal levels of patients with primary aldosteronism. Most hypertensive patients with hypokalemia have secondary rather than primary aldosteronism. The plasma aldosterone-to-plasma renin activity (PRA) ratio (disregarding units of measure) is the most sensitive and specific single screening test for primary aldosteronism. However, because of laboratory variability, normal ranges must be developed for individual laboratory values. A random peripheral blood sample can be used to obtain this ratio even while the patient is receiving antihypertensive medications, when the effects of the medications on PRA and aldosterone are considered. (Data from Weinberger and coworkers [3,4].)

2. Young W. Endocrinology 144(6):2208-2213
Functional Tumors: Primary Aldosteronism

- **Diagnosis & Management:**
  - Once PA is suspected, an imaging study such as CT scan is needed. MRI is often not required.

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![Diagram](image)

**Fig. 3.** Subtype evaluation of primary aldosteronism. See text for details. AVS, Adrenal venous sampling; PAH, primary adrenal hyperplasia. [Modified from W. F. Young, Jr., and M. J. Hogan: *Trends Endocrinol Metab* 5:97–106, 1994 (82), with permission from Elsevier.]
Functional Tumors: Primary Aldosteronism

- **Pharmacologic Treatment:**
  - Utilized for patients with bilateral hyperplasia or glucocorticoid-remediable aldosteronism.

- **Spironolactone:**
  - Antagonist of aldosterone by binding receptors in the distal convoluted renal tubule.
  - Side effect: *gynecomastia* (due to binding testosterone receptors)

- **Eplerenone:**
  - Newer agent. Steroid based with similar class of action.
  - Can be used with an ACE inhibitor.
  - Head to head comparison to Spironolactone has not be done as yet.
Functional Tumors: 
Hypercortisolism (Cushing’s)

**Diagnosis/Clinical Features:**
1. Hypertension
2. “Buffalo hump”
3. Abdominal Striae
4. Abdominal fat distribution.
5. Elevated serum cortisol
6. Incidence: 10 per million.

**FIGURE 4-18** (see Color Plate)
Physical characteristics of Cushing’s syndrome. 

A. Side profile of a patient with Cushing’s syndrome demonstrating an increased cervical fat pad (so-called buffalo hump), abdominal obesity, and thin extremities and petechiae (on the wrist). The round (so-called moon) facial appearance, plethora, and acne cannot be seen readily here.

B. Violecent abdominal striae in a patient with Cushing’s syndrome. Such striae also can be observed on the inner parts of the legs in some patients.
Functional Tumors: Hypercortisolism (Cushing’s)

- Screening Assays

**TABLE 4-23**

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<tr>
<th>Test</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
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<tbody>
<tr>
<td>Elevated PM serum cortisol</td>
<td>=75</td>
<td>=60</td>
</tr>
<tr>
<td>Elevated urinary 17-hydroxy corticosteroids</td>
<td>&gt;90</td>
<td>=60</td>
</tr>
<tr>
<td>Elevated urinary free cortisol</td>
<td>&gt;95</td>
<td>&gt;95</td>
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**FIGURE 4-23**

Screening tests for Cushing’s syndrome. Whereas elevated evening plasma cortisol levels typically indicate abnormal circadian rhythm, other factors such as stress also can cause increased levels late in the day. Urinary levels of 17-hydroxy corticosteroids may be increased in association with obesity. In such cases, repeat measurement after a period of dexamethasone suppression may be required to distinguish this form of increased glucocorticoid excretion from Cushing’s syndrome. The measurement of urinary-free cortisol is the most sensitive and specific screening test.
Functional Tumors: Hypercortisolism (Cushing’s) Diagnostic & Treatment Algorithm

Clinical Suspicion of Cushing’s syndrome

24 hr urinary cortisol (2-3)

No Cushing’s syndrome

Equivocal Cushing’s syndrome

Low-dose dexamethasone suppression test

Cushing’s syndrome

No Cushing’s syndrome

ACTH-Independent Cushing’s syndrome

ACTH-Dependent Cushing’s syndrome

Adrenal CT or MRI

Surgery

Surgery (if operable)

Possible ectopic ACTH syndrome

Matyrpene test; chest CT or MRI

Negative/equivocal

Cushing’s disease

Inferior petrosal sinus sampling w/ CRH test

Pituitary MRI or CT

Surgery

Surgery (if operable)
Functional Tumors: Pheochromocytomas

- Found in .005% to .1% of people.
- Associated with MEN Type 2a & 2b.
- Peak incidence in 4th & 5th decade of life.
- Rules of tens: bilaterality, extra-adrenal in location, familial, multicentric, malignant, pediatric
- Arise from adrenal medulla or extra-adrenal chromaffin tissue (organ of Zuckerkandl).
- Present with hypertension that may be mild to paroxysmal. May also have orthostatic hypotension due to diminished plasma volume.
Figure 4-31
Screening and diagnostic tests in pheochromocytoma. Drugs, incomplete urine collection, and episodic secretion of catecholamines can influence the tests based on 24-hour urine collections in a patient with a pheochromocytoma. The clonidine suppression test is fraught with false-negative and false-positive results that are unacceptably high for the exclusion of this potentially fatal tumor. The “sleep” norepinephrine test eliminates the problems of incomplete 24-hour urine collection because the patient discards all urine before retiring; saves all urine voided through the sleep period, including the first specimen on arising; and notes the elapsed (sleep) time [10]. The sleep period is typically a time of basal activity of the sympathetic nervous system, except in patients with pheochromocytoma (see Fig. 4-32).

Figure 4-33
Localization of pheochromocytoma. Once the diagnosis of pheochromocytoma has been made, it is very important to localize the tumor preoperatively so that the surgeon may remove it with a minimum of physical manipulation. Computed tomographic scan or MRI appears to be the most effective and safest techniques for this purpose [10]. The patient should be treated with α-adrenergic blocking agents for 7 to 10 days before surgery so that the contracted extracellular fluid volume can be expanded by vasodilation.
Functioning Tumors: Androgenital Syndromes

- A constellation of disorders related to a deficiency in an enzyme needed in creating cortisol. ACTH levels increase producing secondary hyperplasia of the adrenal cortex and cortisol precursors are shunted into the androgen pathway.

- Most common is 21-hydroxylase deficiency (>90%). Treatment is glucocorticoid and mineralcorticoid replacement and correction of ambiguous genitalia.

- Virilizing adrenal tumors are seen and may present with hirsutism and masculinization in women. 17-ketosteroid is elevated and used as a marker for disease or recurrence.
Indications for Laparoscopic Adrenalectomy

• Biochemically functioning tumors and potentially malignant tumors of the adrenal gland.

• Biochemically active lesions:
  • Aldosteronomas or unilateral aldosterone producing hyperplastic gland
  • Cortisol elaborating tumors
  • Pheochromocytomas
  • Primary adrenal hyperplasia

• Potentially malignant tumors:
  • Non-functional lesions > 5 cm
  • Suspected adrenal mets
  • Primary adrenocortical carcinomas

Contraindications:
Very large tumors > 10 cm or clearly invasive malignant tumors or other general contraindication to laparoscopic surgery (i.e. severe COPD, untreated coagulopathy).

McKinlay R et al Current Surgery 60(2) Mar-Apr 2003. 145-149
Algorithm for Open vs. Minimally Invasive Adrenalectomy

Adrenal Neoplasm

Functioning

No

Adrenal tumor size

<3 cm

Follow up

No

Adrenalectomy?

Suspicious imaging
Young age
Cancer hx
Growth on f/u
Patient preference

Yes

Adrenalectomy

3-5 cm

Laparoscopic

Localized disease
Few or no signs of malignancy on CT
Small tumors < 6 cm
Metachronous tumors
All Aldosteronomas
Most Pheochromocytomas
Most cortisol, sex-steroid, or mineralcorticoid elaborating tumors

Yes

Open

Imaging c/w invasion
Imaging c/w malignancy
Large tumors > 10 cm
Rapid onset of virilization, feminization or Cushing’s
Multiple elaborated tumors
Family Hx of Malignant Pheochromocytoma

> 5 cm

Adrenalectomy

> 5 cm

Adrenalectomy

Yes

Adrenalectomy

Laparoscopic Approaches

- Transperitoneal Laparoscopic Approach
- Retroperitoneal Laparoscopic Approach
Transperitoneal Approach

- **Positioning:**
  - Induction/intubation/foley insertion: supine
  - Place patient with contralateral side in decubitus.
  - Kidney rest is positioned above iliac crests with bean bag.
  - Operating table is flexed at the patient’s waist to open the angle b/w costal margin and iliac crest.
Transperitoneal Approach

- **Left Adrenalectomy Dissection:**
  - The splenic flexure is dissected and allowed to lie medially with gravity, exposing Gerota’s fascia.
  - The spleen is retracted superiorly, and the distal pancreas is retracted medially exposing the splenic vein and artery.
  - Gerota’s fascia is incised and dissected using cautery or ultrasonic dissection on the lateral border and directed superiorly.
  - Within the inferior pole of the gland lies the adrenal vein which is then clipped and divided. The adrenal arteries are also clipped and divided.
  - Once freely dissected, the specimen is then removed from the operative field.
Retroperitoneal Approach

- More difficult as there is a loss of intra-abdominal landmarks.
- A balloon is inserted in the retroperitoneal space to widen the peri-adrenal space.
- Position: Prone jack-knife with table flexed at waist.
  - Advantages:
    - Require fewer trocars (3 vs. 4 or 5).
    - Lack of intra-abdominal dissection.
    - May reduce intra-operative time (since spleen & splenic flexure dissection is not required).
  - Disadvantages:
    - Limited to small tumors.
    - Technical difficulty.
    - Need to reposition patient if contralateral gland is to be explored.
Complications

- Transabdominal (~7%):
  - Thrombo-embolic (1.2%), post-operative hemorrhage requiring transfusion, (2.1%), UTI (1.2%), PTX (.3%), Superficial SSI at trocar site (.9%), pancreatitis (.3%), pneumonia (.6%), iatrogenic injury to kidney from Veress needle (.3%)

- Retroperitoneal (~5%):
  - Iatrogenic pleural tear (2.5%), hematoma (2.5%)
Open vs. Laparoscopic Resection

- No head to head RCT comparison thus far.
- Retrospective series have demonstrated decreased blood loss, post-operative pain, and LOS.
- One study demonstrated greater operative time, but this may diminish with surgeon experience.

Video
Summary

- Functional adrenal lesions warrant a surgical resection whenever feasible.
- Lesions considered benign are best treated with laparoscopic resection.
- Incidentalomas have increasing risk of harboring malignancy with increasing size and should be excised if > 3 cm in young patients with no comorbidities or >5 cm in older patients.
Additional References

Happy Holidays!