The Work-up and Treatment of Adrenal Nodules

Lawrence Andrew “Drew” Shirley, MD, MS, FACS
Assistant Professor of Surgical-Clinical
Department of Surgery
Division of Surgical Oncology
The Ohio State University Wexner Medical Center

Outline

- Incidentaloma
- Functional Nodules
  - Cushing’s Syndrome
  - Pheochromocytoma
  - Hyperaldosteronism
- Adrenocortical Carcinoma

Incidentaloma

Incidentaloma - Epidemiology

- Autopsy studies – 1.1 - 32% (avg 5.9%)
- Imaging studies:
  - 1,459 patients – 4.3%
  - 61,054 patients – 3.4%
Incidental Adrenal Mass

• Is it functional?

Is it malignant?
(Primary or metastatic)

Incidental Adrenal Mass Work-up

• Thorough history and physical exam
  • HTN, weight change, diabetes, appearance change, malignancy, family history

• Serum potassium, aldosterone, and renin
Incidental Adrenal Mass Work-up

- Thorough history and physical exam
  - HTN, weight change, diabetes, appearance change, malignancy, family history
- Serum potassium, aldosterone, and renin
- 24 hour urinary cortisol or low dose dexamethasone suppression test

Next question: Is it malignant?

- Larger the tumor, the greater the cancer risk

Next question: Is it malignant?

- Larger the tumor, the greater the cancer risk
  - Generally recommended if 4 – 5 cm or greater then resect
Next question: Is it malignant?

• Larger the tumor, the greater the cancer risk
• Generally recommended if 4 – 5 cm or greater then resect
• If metastatic disease possible – consider FNA

Next question: Is it malignant?

• Larger the tumor, the greater the cancer risk
• Generally recommended if 4 – 5 cm or greater then resect
• If metastatic disease possible – consider FNA
• Before FNA – MUST RULE OUT PHEO!

Size

• Masses > 6 cm – Greater >25% Malignant
• Masses < 4 cm Are Generally Monitored
  • Q 6 month imaging x 2
  • Q yr hormonal study x 4
• For Masses Between 4 and 6 cm:
  *Criteria other than size should be considered in making the decision to monitor or to proceed to operation.*

Adrenal Protocol CT Scans

• Initial HU without contrast:
  Adenomas: < 10 HU (lipid rich)
  Malignancies: > 18 HU
  Sensitivity: 73% Specificity: 96%
• Washout 10 – 15 minutes after contrast:
  Adenomas: > 60%
  Sensitivity: 88% Specificity: 96 -100%
• Worrisome features: Irregular, inhomogeneous enhancement, central necrosis, calcification in 30%, local invasion
MRI

- Equally Effective As CT
- Adenomas Are Iso-Intense With The Liver On T2-weighted Images
- Carcinomas Have A Hyper-Intense Signal Compared With The Liver On T2

Fine-Needle Aspiration Biopsy

- FNA is indicated for pts with possible metastatic disease to adrenal or for lymphoma diagnosis
- CANNOT Distinguish A Benign Adrenal Mass From Adrenocortical Carcinoma
- Unnecessary FNA is a common pitfall in working up an adrenal incidentaloma
  - Potentially dangerous
  - Rarely alters management

Evaluation of Incidentaloma

- History and Physical
  - Determine Function
    - Non-Functional
    - Functional
      - Size
        - < 4 cm
        - > 4 cm
          - Surgery
          - Observe (serial exams)
Cushing’s Syndrome

Harvey Cushing

- Born in Cleveland – 1869
- Educated at Yale
- House staff at Johns Hopkins
- Peter Brent Brigham Hospital
  1912 – 1932
- Dr. W. T. Bovie develop electrocautery - 1926

- 1912 described Minnie G.
  - Multiglandular disease

- 1932 reports on 12 patients
  - Pituitary Basophilism
Harvey Cushing

- 1912 described Minnie G.
  - Multiglandular disease
- 1932 reports on 12 patients
  - Pituitary Basophilism
- Bishop and Close named the disease “Cushing’s syndrome”

Hypothalamus – Pituitary – Adrenal Axis

Clinical Manifestations

Clinical Manifestations
Cushing’s Syndrome - Etiology

- ACTH dependent – 90%
  - Pituitary (Cushing’s disease) or ectopic
  - ACTH independent – 10%
  - Adrenal

Cushing’s Syndrome - Diagnosis

- Establish abnormal cortisol production
  - 24 hour urine for free cortisol and creatinine
  - Low-dose dexamethasone test – 1 mg at 11pm, measure cortisol at 8 am (nl < 5 ug/dl)
  - Midnight salivary cortisol – correlates well with serum cortisol, lowest levels at midnight

- Next establish cause ⇒ Serum ACTH
  - if > 15 then ACTH dependent (pituitary, ectopic)
  - if < 5 ACTH independent (adrenal)

Cushing’s Syndrome - Treatment

- ACTH Dependent
  - Treat cause
  - Rarely bilateral adrenalectomies

- ACTH Independent
  - Laparoscopic/Robotic adrenalectomy
  - Exogenous steroids for several months to a year for HPA axis recovery
Subclinical Cushing’s Syndrome

- 20% develop overt clinical Cushing over time
- At risk for post-operative Addison’s
  - 40 – 100%
- Associated with increased incidence of:
  - HTN, Obesity, DM, Cardiovascular dz, Decreased bone density (controversial)
- Surgery Improves
  - Weight 55 – 100%
  - HTN 57 – 100%
  - Glucose control 50 – 100%

Pheochromocytoma

- Secrete catecholamines (epinephrine, norepinephrine, dopamine)
- No longer 10% tumor – malignancy 20% and inherited 25%
Pheochromocytoma

- Secrete catecholamines (epinephrine, norepinephrine, dopamine)
- No longer 10% tumor – malignancy 20% and inherited 25%
- Hallmark is hypertension
  - Paroxysmal HTN - 30%
  - Sustained HTN – 50%
  - No HTN – 20%

Pheochromocytoma

- Not possible to determine which will present with crisis

Pheochromocytoma

- Not possible to determine which will present with crisis
- 19-76% of pheochromocytomas not diagnosed until after death
- Previously reported 80% mortality in patients with unsuspected pheochromocytomas who undergo surgery or anesthesia
**Pheochromocytoma - Diagnosis**

- 24 hour urinary catecholamines – epinephrine, norepinephrine, metanephrine, VMA
  - Beta-blockers and tricyclics – false positive

**Pheochromocytoma - Diagnosis**

- 24 hour urinary catecholamines – epinephrine, norepinephrine, metanephrine, VMA
  - Beta-blockers and tricyclics – false positive
  - Plasma metanephrines
    - Affected by caffeine, tobacco, theophylline, alcohol, acetaminophen, and sinus medications

**Pheochromocytoma - Imaging**

- CT scan
- MRI
- MIBG scan

Must be done prior to FNA of any adrenal mass!
Pheochromocytoma - Imaging

- CT scan
- MRI
- MIBG scan

CT most cost-effective, MRI more sensitive, and MIBG more specific

MIBG indications

- Risk for multiple tumors, extra-adrenal tumors, metastases
- Young pts and those with syndromes
- Persistent/recurrent malignant disease
- Overall Sensitivity 87%, Specificity 100%
  - Sensitivity higher for malignant pheo and familial pheo as opposed to sporadic

Pheochromocytoma - Preoperative Preparation

- Alpha-blockade (FIRST)
  - Doxazosin 2mg QHS
  - Phenoxybenzamine 10 mg BID
  - Titrate up to orthostatic tachycardia or hypotension

Pheochromocytoma - Preoperative Preparation

- Alpha-blockade (FIRST)
  - Doxazosin 2mg QHS
  - Phenoxybenzamine 10 mg BID
  - Titrate up to orthostatic tachycardia or hypotension
- Beta-blockade (SECOND)
  - For resting tachycardia
Pheochromocytoma - Preoperative Preparation

- Alpha-blockade (FIRST)
  - Doxazosin 2mg QHS
  - Phenoxybenzamine 10 mg BID
  - Titrate up to orthostatic tachycardia or hypotension
- Beta-blockade (SECOND)
  - For resting tachycardia

Treatment: Laparoscopic/Robotic adrenalectomy

Treatment of Malignant Pheochromocytoma

- Incidence of malignancy may be closer to 30-50% than 10%
- Resect localized recurrences or mets
- Painful bony mets respond well to radiotherapy
- Chemo:
  - Standard chemo regimens have limited efficacy
- Iodine-131 MIBG therapy:
  - In pts whose tumors are imaged by MIBG
  - Reported response rate of 60%

Hyperaldosteronism

Angiotensinogen to Angiotensin I

Circulating Blood Volume

Aldosterone

Angiotensin II

Adrenal Cortex

Renin
Primary Hyperaldosteronism

- Hypertension, hypokalemia, and metabolic alkalosis
- Generally underdiagnosed

Primary Hyperaldosteronism

- Hypertension, hypokalemia, and metabolic alkalosis
- Generally underdiagnosed
- Previously experts thought
  - <1% of HTN patients
  - hypokalemia *sin qua non*
### Primary Hyperaldosteronism

- **Hypertension, hypokalemia, and metabolic alkalosis**
- Generally underdiagnosed
- Previously experts thought
  - <1% of HTN patients
  - hypokalemia *sin qua non*
- **Currently**
  - 5 – 10% of HTN patients
  - Only 10 – 40% hypokalemia

### Primary Hyperaldosteronism - Etiology

- Aldosterone-producing adenoma (APA or Conn’s syndrome)
  - Typically small: <2 cm
  - Corrected by surgery
- Idiopathic hyperaldosteronism (IAH)
  - Bilateral adrenal hyperplasia or nodules
  - Not cured by surgery
  - Life long medical treatment – spironolactone, eplerenone

### Primary Hyperaldosteronism - Diagnosis

- Aldosterone – Renin ratio (ARR)
  - Hyperaldo if ARR is greater than 20 (nl <10) especially if aldo level > 15
  - Ideally blood drawn mid morning
  - Stop spironolactone, eplerenone, amiloride, and triamterene for 4 weeks
- Saline Suppression test
  - Infuse 2 liters saline over 4 hours – normally aldo should drop to <5
  - (>10 consistent with hyperaldo)
### Adenoma vs. Hyperplasia

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• Very High PAC/PRA</strong></td>
<td><strong>Adenoma</strong></td>
</tr>
<tr>
<td><strong>• Measure morning 18-</strong></td>
<td></td>
</tr>
<tr>
<td><strong>hydrocorticosterone</strong></td>
<td></td>
</tr>
<tr>
<td><strong>• Typically level &gt; 100 for APA</strong></td>
<td></td>
</tr>
</tbody>
</table>

### Adrenal Vein Sampling

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• Gold-standard distinguishing APA and IAH</strong></td>
<td></td>
</tr>
<tr>
<td><strong>• Challenging procedure: cannulating right adrenal vein difficult (directly off IVC)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>• Successful 75 – 95% depending on experience</strong></td>
<td></td>
</tr>
<tr>
<td><strong>• Consider for all pts age &gt; 40, equivocal CT</strong></td>
<td></td>
</tr>
<tr>
<td><strong>• Findings or equivocal diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>• Measure aldosterone and cortisol</strong></td>
<td></td>
</tr>
<tr>
<td><strong>simultaneously to confirm placement and dilution</strong></td>
<td></td>
</tr>
<tr>
<td><strong>(phrenic and renal on left), also use ACTH (cosyntropin)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>• Typical APA aldo/cort ratio &gt;3 – 4 times higher</strong></td>
<td></td>
</tr>
<tr>
<td><strong>than contralateral side</strong></td>
<td></td>
</tr>
</tbody>
</table>

### Primary Hyperaldosteronism - Treatment

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• Laparoscopic/Robotic adrenalectomy</strong></td>
<td></td>
</tr>
<tr>
<td><strong>• Results</strong></td>
<td></td>
</tr>
<tr>
<td><strong>• Hypokalemia resolves</strong></td>
<td></td>
</tr>
<tr>
<td><strong>• Hypertension improves</strong></td>
<td></td>
</tr>
</tbody>
</table>

### Adrenocorticol Carcinoma

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
</table>
Adrenocortical Carcinoma

- Multiple or mixed hormone secretion is highly suspicious for malignancy
- Measure DHEA-sulfate and total testosterone
- Most sporadic, but can be familial
  - Li-Fraumeni, Carney Complex, Beckwith-Wiedemann, FAP, MEN1
  - Consider TP53 testing in all patients

Adrenocortical Carcinoma - Treatment

- Surgical Resection – OPEN
- Metastatic work-up preoperatively
- Mitotane 15 – 22% response rate
- Combination cytotoxic chemotherapy
- Consider radiotherapy locally
Adrenocortical Carcinoma - Prognosis

- Depends on Stage and Complete Resection
- < 50% ACC localized to adrenal only
- Overall, 22% 5-yr survival for resected
- <10% 1-year survival for Stage IV disease
- About 2/3 develop recurrence within 2 years