Management of Incidental Adrenal Lesions

Tommy Johnston
PCH Urology Audit Meeting
16/2/15
Adrenal Incidentaloma’s (AI’s)

Definition
Adrenal mass > 1cm in diameter discovered incidentally when investigating for something else

Widespread use of USS, CT and MRI has resulted in a dilemma for clinicians

Prevalence
- Autopsy studies (87,000) reported frequency of 6% (range 1-32%)
- Abdominal CT’s series overall prevalence of 4%
- Risk increases with age
  - 20 -29 years = 0.2%
  - 70+ years = 7%
- CT series in pt’s with extra-adrenal malignancy 6-20%
Adrenal Incidentaloma’s

Majority are non-hypersecreting, benign adenomas (85%)

Adrenal hypersecreting or hormonally active (15%)
- Phaeochromocytoma (5-8%)
- Cushing syndrome (5%)
- Conn’s syndrome (1%)
- Androgen secreting tumours (<1%)

What are the chances of it being malignant?
- < 5% chance of it being a primary adrenal tumour
- < 1% of it being a metastasis if no prior Hx of primary cancer

Consensus view that all AI’s should include thorough clinical, biochemical and radiological assessment
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing’s syndrome</td>
<td>Patient may be asymptomatic if disease is subclinical; symptoms may include weight gain with central obesity, facial rounding and plethora, supraclavicular and dorsocervical fat pads, easy bruising, thin skin, poor wound healing, purple striae, proximal muscle weakness, emotional and cognitive changes (e.g., irritability, spontaneous tearfulness, depression, and restlessness), opportunistic and fungal infections, altered reproductive function, acne, and hirsutism</td>
<td>Hypertension, osteopenia, osteoporosis, fasting hyperglycemia, diabetes mellitus, hypokalemia, hyperlipidemia, and leukocytosis with relative lymphopenia</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Patient may be asymptomatic; episodic symptoms may occur in spells (paroxysms) that can be extremely variable in presentation but typically include forceful heartbeat, pallor, tremor, headache, and diaphoresis; spells may be either spontaneous or precipitated by postural change, anxiety, medications (e.g., metoclopramide, anesthetic agents), and maneuvers that increase intraabdominal pressure (e.g., change in position, lifting, defecation, exercise, colonoscopy, pregnancy, and trauma)</td>
<td>Hypertension (paroxysmal or sustained), orthostatic hypotension, pallor, retinopathy grades 1 to 4, tremor, and fever</td>
</tr>
<tr>
<td>Primary aldosteronism</td>
<td>If hypokalemia is present, nocturia, polyuria, muscle cramps, and palpitations may be present</td>
<td>Hypertension, mild or severe; possibly hypokalemia and mild hypernatremia</td>
</tr>
<tr>
<td>Adrenocortical carcinoma</td>
<td>Symptoms may include mass effect (e.g., abdominal pain) and symptoms related to adrenal hypersecretion of cortisol (Cushing’s syndrome), androgens (hirsutism, acne, amenorrhea or oligomenorrhea, oily skin, and increased libido), estrogens (gynecomastia), or aldosterone (hypokalemia-related symptoms)</td>
<td>Hypertension, osteopenia, osteoporosis, fasting hyperglycemia, diabetes mellitus, hypokalemia, hyperlipidemia, and leukocytosis with relative lymphopenia</td>
</tr>
<tr>
<td>Metastatic cancer</td>
<td>History of an extraadrenal cancer</td>
<td>Cancer-specific signs</td>
</tr>
</tbody>
</table>
Biochemical assessment

1. **24 hour catecholamines/metanephrines** (Phaeochromocytomas)
   - Sensitivity 95% and specificity of 95%
   - Fractionated metanephrines 98% sensitive (only used to confirm Dx)

2. **Overnight 1mg Dexamethasone suppression test**
   - Sensitivity 70-100% and specificity of 90%
   - Test of choice to rule out Cushing’s or Sub-clinical Cushing’s syndrome
   - > 138nmol/l = Cushing’s if clinical features or Sub-clinical if no symptoms
   - **Note** subset of Cushing’s syndrome pt’s may have normal results

3. **Aldosterone – renin ratio**
   - Sensitivity 90% and specificity of 90%
   - Best test for Conn’s syndrome (ARR high or high normal)
   - Must stop B-blockers (false positives) and aldosterone antagonists (false negatives)

**Confirmatory hormonal testing is recommended in all +ve screening tests to limit false positive results and unnecessary surgery**
Radiological Assessment

Computer tomography
- Risk of adrenal cancer related to size: <2cm = 2%; 4-6cm = 6%; 6cm+ = 25%
- Calcifications, haemorrhage and necrosis rarely seen in benign adenoma’s
- Characteristic malignant/phaechromocytomas features:
  - Size > 3cm
  - Heterogeneous texture
  - Increased vascularity
  - Attenuation of > 10 HU on unenhanced CT
  - Decreased contrast washout at 10 – 15mins (< 50%)
  - Overlap between benign and malignant in 10 – 30% (indeterminate)

- Benign adenoma’s:
  - < 10HU (98% specific for benign) as usually greater proportion of fat
  - > 50% washout10mins of contrast medium has sensitivity and specificity of 95-98% for benign

Note: No role for MRI if use contract washout protocol on CT
## Table 3. Characteristics of Adrenal Incidentalomas on Imaging (Imaging Phenotype).*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adrenocortical Adenoma</th>
<th>Adrenocortical Carcinoma</th>
<th>Pheochromocytoma</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Small, usually ≤3 cm in diameter</td>
<td>Large, usually &gt;4 cm in diameter</td>
<td>Large, usually &gt;3 cm in diameter</td>
<td>Variable, frequently &lt;3 cm</td>
</tr>
<tr>
<td>Shape</td>
<td>Round or oval, with smooth margins</td>
<td>Irregular, with unclear margins</td>
<td>Round or oval, with clear margins</td>
<td>Oval or irregular, with unclear margins</td>
</tr>
<tr>
<td>Texture</td>
<td>Homogeneous</td>
<td>Heterogeneous, with mixed densities</td>
<td>Heterogeneous, with cystic areas</td>
<td>Heterogeneous, with mixed densities</td>
</tr>
<tr>
<td>Laterality</td>
<td>Usually solitary, unilateral</td>
<td>Usually solitary, unilateral</td>
<td>Usually solitary, unilateral</td>
<td>Often bilateral</td>
</tr>
<tr>
<td>Attenuation (density) on unenhanced CT</td>
<td>≤10 Hounsfield units</td>
<td>&gt;10 Hounsfield units (usually &gt;25)</td>
<td>&gt;10 Hounsfield units (usually &gt;25)</td>
<td></td>
</tr>
<tr>
<td>Vascularity on contrast-enhanced CT</td>
<td>Not highly vascular</td>
<td>Usually vascular</td>
<td>Usually vascular</td>
<td></td>
</tr>
<tr>
<td>Rapidity of washout of contrast medium</td>
<td>≥50% at 10 minutes</td>
<td>&lt;50% at 10 minutes</td>
<td>&lt;50% at 10 minutes</td>
<td></td>
</tr>
<tr>
<td>Appearance on MRI†</td>
<td>Isointense in relation to liver on T₂-weighted image</td>
<td>Hyperintense in relation to liver on T₂-weighted image</td>
<td>Markedly hyperintense in relation to liver on T₂-weighted image</td>
<td>Hyperintense in relation to liver on T₂-weighted image</td>
</tr>
<tr>
<td>Necrosis, hemorrhage, or calcifications</td>
<td>Rare</td>
<td>Common</td>
<td>Hemorrhage and cystic areas common</td>
<td>Occasional hemorrhage and cystic areas</td>
</tr>
<tr>
<td>Growth rate</td>
<td>Usually stable over time or very slow (&lt;1 cm per year)</td>
<td>Usually rapid (&gt;2 cm per year)</td>
<td>Usually slow (0.5 cm to 1.0 cm per year)</td>
<td>Variable, slow to rapid</td>
</tr>
</tbody>
</table>
Other assessment tools

**PET**
- Useful in detecting metastasis in patients with previous oncological Hx
- Metabolically active lesions take up FDG versus benign lesions

**Fine-needle aspiration cytology**
- Not recommended for routine workup
- Most commonly used for Al’s in pt’s with Hx of extra-adrenal disease
- MUST exclude phao first as risk of hypertensive crisis or severe haemorrhage
Management

Adrenalectomy
- Functioning tumour
- Non-functioning tumour > 4cm
- Non-functioning tumour < 4 cm with calcification, haemorrhage or necrosis
- Non-functioning tumour with positive PET or FNAC if solitary
- Must take into account patient age, co-morbidities and clinical judgement

Follow-up for non-functioning with favourable CT features
- Use clinical judgement when assessing 4 – 6cm size
- Re-imaging at 3 – 6, 12 and 24 months
- Repeat hormones annually
- If no change after 24 months, discharge
- If increase > 1cm or becomes hormonally active, surgery

Note: 2 – 8% non-functional to functional in 2 years in Al’s > 3cm
Growth rate > 1cm in 5 – 25% of Al’s, of which 5% will malignant when excised
Guidelines for the management of the incidentally discovered adrenal mass

Anil Kapoor, MD, FRCSC; Topher Morris, BMS c; Ryan Rebbello, MD, FRCSC

*Division of Urology, Department of Surgery, McMaster University, Hamilton, ON; †Department of Radiology, McMaster University, Hamilton, ON

### Table 1. Long-term follow-up of adrenal incidentalomas

<table>
<thead>
<tr>
<th>Study</th>
<th>Average mass size (cm)</th>
<th>Follow-up years [range]</th>
<th>Mass increase</th>
<th>Mass decrease</th>
<th>Malignancy</th>
<th>Hyperfunction</th>
<th>Overt disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giordano et al. 2010</td>
<td>2.22</td>
<td>3 (1-10)</td>
<td>7/118</td>
<td>2/118</td>
<td>0/118</td>
<td>0/102</td>
<td>0/118</td>
</tr>
<tr>
<td>Comlekci et al. 2010</td>
<td>2.5</td>
<td>2 (0.5-11)</td>
<td>30/162</td>
<td>8/162</td>
<td>0/162</td>
<td>6/162</td>
<td>0/162</td>
</tr>
<tr>
<td>Vassilatou et al. 2009</td>
<td>2.5</td>
<td>5.2 (1-12.8)</td>
<td>20/77</td>
<td>6/77</td>
<td>0/77</td>
<td>NC</td>
<td>4/77</td>
</tr>
<tr>
<td>Fagour et al. 2009</td>
<td>2.4</td>
<td>4.3 (2.7-5.9)</td>
<td>5/51</td>
<td>1/51</td>
<td>0/51</td>
<td>3/27a</td>
<td>3/51</td>
</tr>
<tr>
<td>Tsvetov et al. 2007</td>
<td>2.6</td>
<td>2</td>
<td>11/88</td>
<td>0/88</td>
<td>1/88</td>
<td>0/88</td>
<td>0/88</td>
</tr>
<tr>
<td>Bulow et al. 2006</td>
<td>2.5</td>
<td>2.1 (0.3-9)</td>
<td>17/229</td>
<td>12/229</td>
<td>0/229</td>
<td>4/229</td>
<td>3/229</td>
</tr>
<tr>
<td>Bernini et al. 2005</td>
<td>2.5</td>
<td>4 (1-7)</td>
<td>32/115</td>
<td>24/115</td>
<td>0/115</td>
<td>NC</td>
<td>0/115</td>
</tr>
<tr>
<td>Emral et al. 2003</td>
<td>NG</td>
<td>2</td>
<td>0/60</td>
<td>0/60</td>
<td>0/60</td>
<td>0/60</td>
<td>0/60</td>
</tr>
<tr>
<td>Libe et al. 2002</td>
<td>2.5</td>
<td>2 (1-10)</td>
<td>13/64</td>
<td>0/64</td>
<td>1/64b</td>
<td>0/64</td>
<td>0/64</td>
</tr>
<tr>
<td>Barzon et al. 2002</td>
<td>3.6</td>
<td>4.6 (1-12)</td>
<td>19/130</td>
<td>2/130c</td>
<td>0/130</td>
<td>6/130</td>
<td>4/130</td>
</tr>
<tr>
<td>Grossrubatscher et al. 2001</td>
<td>2.5</td>
<td>2.0 (0.5-6.5)</td>
<td>22/53</td>
<td>6/53</td>
<td>0/53</td>
<td>0/53</td>
<td>0/53</td>
</tr>
<tr>
<td>Favia et al. 2000</td>
<td>4.4</td>
<td>2.8 (0.5-5)</td>
<td>NG</td>
<td>0/90</td>
<td>0/90</td>
<td>0/90</td>
<td>0/90</td>
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<tr>
<td>Rossi et al. 2000</td>
<td>3.26</td>
<td>2.8 (0.5-7.1)</td>
<td>7/32</td>
<td>0/32</td>
<td>0/32</td>
<td>1/32</td>
<td>0/32</td>
</tr>
<tr>
<td>Siren et al. 2000</td>
<td>2.5</td>
<td>7.1 (2-16.3)</td>
<td>4/27</td>
<td>7/27</td>
<td>0/27</td>
<td>0/27</td>
<td>0/27</td>
</tr>
<tr>
<td>Mantero et al. 2000</td>
<td>NG</td>
<td>&gt;1</td>
<td>14/53</td>
<td>0/53</td>
<td>0/53</td>
<td>1/53</td>
<td>1/53</td>
</tr>
<tr>
<td>Terzolo et al. 1998</td>
<td>2.5</td>
<td>&gt;1</td>
<td>0/53</td>
<td>0/53</td>
<td>0/53</td>
<td>0/53</td>
<td>0/53</td>
</tr>
<tr>
<td>Barry et al. 1998</td>
<td>3.2</td>
<td>7.0 (0.1-11.7)</td>
<td>4/91</td>
<td>0/91</td>
<td>0/224</td>
<td>0/224</td>
<td>0/224</td>
</tr>
<tr>
<td>Terzolo et al. 1997</td>
<td>NG</td>
<td>1</td>
<td>1/41</td>
<td>0/41</td>
<td>0/41</td>
<td>0/41</td>
<td>0/41</td>
</tr>
<tr>
<td>Bastounis et al. 1997</td>
<td>3.2</td>
<td>3.6 (1-5.3)</td>
<td>2/60</td>
<td>0/60</td>
<td>0/60</td>
<td>0/60</td>
<td>0/60</td>
</tr>
<tr>
<td>Bencsik et al. 1995</td>
<td>&lt;3</td>
<td>1.5 (0.3-3.4)</td>
<td>1/27</td>
<td>0/27</td>
<td>0/27</td>
<td>0/27</td>
<td>0/27</td>
</tr>
<tr>
<td>Herrera et al. 1991</td>
<td>NG</td>
<td>2.0 (0.1-5.6)</td>
<td>5/159</td>
<td>4/159</td>
<td>0/159</td>
<td>0/287</td>
<td>NG</td>
</tr>
</tbody>
</table>

| Total                      | 212/1690               | 72/1690                 | 1/1913        | 21/1809       | 15/1754    |
|                           | 12.5%                  | 4.3%                    | 0.05%         | 1.2%          | 0.9%       |
Case studies

**Patient 1** - 48F with ? appendicitis
CT - Right contrast-enhanced 4.5 cm in diameter
Heterogeneous (vascular)
Unenhanced CT attenuation was 40 HU
Contrast-medium washout < 50%/10 mins
No symptoms or signs of pheochromocytoma
Both urine/plasma elevated normetanephrine levels

**Patient 2** - 62F with abdominal pain
CT - Right adrenal 3.6 cm x 2.5 cm mass
Unenhanced CT attenuation was < 10 HU
Contrast-medium washout > 50%/10 mins
Negative urine/plasma normetanephrine levels
Case studies

**Patient 3** - 27F flushing and loose stools
CT - Left adrenal mass 7 x 5 x 6 cm
  - Heterogenous and contrast enhancing
  - Unenhanced CT attenuation was > 10 HU
  - Contrast-medium washout < 50%/10 mins
Non-functioning on hormonal testing
Management Algorithm

History and physical examination
Hormonal testing
  Overnight dexamethasone (1 mg) suppression test
  Measurement of fractionated metanephrines and catecholamines in a 24-hr urinary specimen
  If hypertension present, measurement of the plasma aldosterone concentration and plasma renin activity

Positive results

Confirmatory testing

Confirmation of autonomous secretion of cortisol, aldosterone, or catecholamines

Consider:
Surgery

Negative results
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The Incidentally Discovered Adrenal Mass
William F. Young, Jr., M.D.

AACE/AAES Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
AND AMERICAN ASSOCIATION OF ENDOCRINE SURGEONS
MEDICAL GUIDELINES FOR THE MANAGEMENT OF ADRENAL INCIDENTALOMAS