Adrenal Incidentalomas

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Case Presentation

- Patient is a 65 year old male who presented to my clinic after an extensive work up by surgery and GI for the evaluation of his chronic abdominal pain.

- The patient was reported at that time to have ongoing pain for the last 2 years with known biliary dyskinesia and chronic hepatitis C.

- The abdominal pain was evaluated initially by CT scan and in addition to gallbladder thickening it showed a 1.3 cm low density adrenal mass.

- During the evaluation by surgery the patient was reported to have a chronic rash for which he has seen Dermatology and thus far no diagnosis was made.
Case Presentation

- The rash was generalized and became brighter red over a period of 3-4 days and then after about 4 days began to peel, finally resulting in desquamation of his skin.

- This cycle occurs about 3 times per year and is always followed by healing of the skin.

- He denies any sweating or tachycardia. He has no anxiety or feelings of impending doom.

- He has a history of mild but treated hypertension.
Case Presentation

- PMH:
  - Chronic Hepatitis C
  - Chronic diverticulitis
  - Insomnia
  - Rash with desquamation
  - Hypertension
  - COPD
  - Depression
Case Presentation

- **PSH**
  - Nasal septal fracture with repair
  - Appendectomy
  - Inguinal hernia repair

- **Social/Habits**
  - Retired painter
  - History of smoking, quit in 1971
  - No alcohol use
Case Presentation

Medications:
- Vitamin D3 3000 units per day
- Albuterol Sulfate inhaler PRN
- Amitriptyline 150 mg qHS

Allergies:
- No medication allergies
- Animal dander
Case Presentation

- Surgery Diagnosis and Plan
  - Colonoscopy with conservative management of diverticulitis.
  - 24 hour urine for Catecholamines and Metanephrines, 5-HIAA.
  - Plasma Metanephrine/Normetanephrines
Case Presentation

Lab results

- Na: 137
- K: 3.7
- BUN: 15
- Crt: 0.95
- Plasma Metanephrine: 0.51 (0-0.49)
- Plasma Normetanephrine: 1.12 (0-0.89)
## Case Presentation

**Urine**

- **Epinephrine**: 7 (0-12)
- **Norepinephrine**: 228 (16-71)
- **Metanephrine**: 270 (62-207)
- **Normetanephrine**: 753 (125-510)
Case Presentation

Imaging
- Chest CT 2012: shows left adrenal mass: Not reported
- Abdominal MRI (Jan 2016): Low density left adrenal mass 20 mm diameter
- CT Abdomen (3/2016): 1.3 cm left adrenal mass -16 HU on pre-contrast images.
"Incidentaloma"

**Definition**
- Adrenal mass discovered accidentally during the evaluation and imaging of a patient for a reason other than adrenal physiology or cancer.

**Autopsy studies** suggest the incidence of incidental adrenal masses to be 8.7%.

**Incidence is increasing**
Diagnostic Goal

- To determine which patients have real disease and to minimize long term complications from functional adenomas.

- In the end, the point of evaluating patients with an adrenal incidentaloma is to rule out Adrenal Cortical Carcinoma.
  - 5 year mortality is approximately 56%.
  - Risk of ACC is based on nodule size
    - <4 cm = 2%
    - 4-6 cm = 6%
    - >6 cm = 25%
“Incidentaloma”

During the evaluation of an adrenal mass, 3 questions need to be addressed:

- Is the tumor hormonally active?
- Does it have radiologic characteristics suggestive of a malignant lesion?
- Does the patient have a history of a previous malignant lesion?
Adrenal Incidentaloma by Disease type

- Nonfunctioning
- Miscellaneous
- Cushing's
- Primary Aldo
- Pheo
- Adrenal Ca
“Incidentaloma”

- **Pathology of Incidentalomas**
  - 80% Nonfunctioning adenoma
  - 5% Subclinical Cushing syndrome
  - 5% Pheochromocytoma
  - 1% Aldosterone secreting adenoma
  - <5% Adrenocortical carcinoma (ACC)
  - 2.5% Metastatic lesion
  - Myelolipoma: Some reports as high as 10%
  - The remaining incidentalomas were ganglioneuromas, or benign cysts.
Before sending a patient to surgery it is important to remember that adrenal surgery is not a simple surgery and the current collection of imaging and laboratory criteria are pretty sensitive the and the standard guidelines should be respected.
Fig. 1. Algorithm for the evaluation and management of an adrenal incidentaloma. * = Reimage in 3 to 6 months and annually for 1 to 2 years; repeat functional studies annually for 5 years. If mass grows more than 1 cm or becomes hormonally active, then adrenalectomy is recommended. CT = computed tomographic; HU = Hounsfield units; PAC = plasma aldosterone concentration; PRA = plasma renin activity.
Workup

- Imaging and biochemical analysis is the mainstay for the evaluation of an incidental adrenal mass.

- In symptomatic patients where the clinical history leads us down a path of screening patients for disease biochemical analysis is always first in the algorithm.

- However, in a patient with an already discovered adrenal mass we should focus first on making sure we have the appropriate information from imaging.
CT scan is historically the imaging of choice for the evaluation of the adrenal nodule.

- Most of the time the CT reports suggest the idea of a follow up MRI but a CT that is done correctly is usually adequate for the characterization of the adrenal mass.
- The exception in this case is the patient who has a high pretest probability of having a pheochromocytoma, in which case an MRI is the imaging modality of choice.
CT Characteristics of Adrenal Masses

■ The pre-contrast density of the adrenal mass is a vital piece of information in the diagnosis of adrenal masses.
  ■ The Hounsfield Units are a direct measurement of the density of an adrenal mass and can be both negative and positive.
  ■ Distilled water is defined as zero Hounsfield units (HU), while the radiodensity of air at STP is defined as -1000 HU.
## Hounsfield Units

<table>
<thead>
<tr>
<th>Substance</th>
<th>HU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>-1000</td>
</tr>
<tr>
<td>Lung</td>
<td>-500</td>
</tr>
<tr>
<td>Fat</td>
<td>-100 to -50</td>
</tr>
<tr>
<td>Water</td>
<td>0</td>
</tr>
<tr>
<td>CSF</td>
<td>15</td>
</tr>
<tr>
<td>Kidney</td>
<td>30</td>
</tr>
<tr>
<td>Blood</td>
<td>+30 to +45</td>
</tr>
<tr>
<td>Muscle</td>
<td>+10 to +40</td>
</tr>
<tr>
<td>Grey matter</td>
<td>+37 to +45</td>
</tr>
<tr>
<td>White matter</td>
<td>+20 to +30</td>
</tr>
<tr>
<td>Liver</td>
<td>+40 to +60</td>
</tr>
<tr>
<td>Soft Tissue, Contrast</td>
<td>+100 to +300</td>
</tr>
<tr>
<td>Bone</td>
<td>+700 (cancellous bone) to +3000 (cortical bone)</td>
</tr>
</tbody>
</table>

Lesions that have an attenuation value below +10 HU on pre-contrast CT scan are adenomas.

Don’t let the word benign adenoma fool you.

Adenomas can be both functional and nonfunctional adrenal masses.

Adenomas constitute about 86-90% of adrenal masses seen in the clinical setting.
The differential diagnosis can be further delineated by CT scans done immediately after intravenous administration of a contrast agent and then again after a 10- to 15-minute delay.

Benign adrenal lesions will commonly enhance up to +80 to +90 HU and washout more than 50% on the delayed scan, whereas lesions such as metastatic tumors, carcinomas, or Pheochromocytomas will not have a rapid washout.
Imaging

- Pheochromocytomas usually show enhancement to more than 100 HU, diagnostically separating them from adenomas.

- On noncontrast CT, some benign adrenal lesions do not have attenuation values of less than 10 HU and may have values of 20 to 40 HU. This result is found in lipid poor adenomas.

- In these cases, a washout of >50% will often allow the diagnosis of an adenoma to be made.
Imaging

- Adrenal masses with HU in the range of -40 and lower are often times read as adrenal myolipomas and are benign by nature despite their size.

- The danger of adrenal myolipomas are their risk of internal hemorrhage at larger sizes.
You have to contact radiology or specify in your orders to radiology in both facilities that you want densities reported.
PET imaging in Adrenal nodules

- PET imaging is relatively new for the evaluation of adrenal nodules but looks promising.
- For combined PET/CT data, the sensitivity, specificity, positive predictive value, and negative predictive value were 100%, 98%, 97%, 100%, respectively.
  - Pheochromocytoma: Low uptake
  - Benign adenoma: Low uptake
  - ACC: High uptake
  - Metastatic Disease: High uptake
# Characteristics of Adrenal Nodules

<table>
<thead>
<tr>
<th>FINDING</th>
<th>Benign adenoma</th>
<th>ACC</th>
<th>Pheochromocytoma</th>
<th>Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>Usually &lt;4cm</td>
<td>Usually &gt;4cm</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Growth rate</strong></td>
<td>Stable or &lt;0.8cm/year</td>
<td>Significant growth (&gt;1cm/year)</td>
<td>Slow growth</td>
<td>Significant growth (&gt;1cm/year)</td>
</tr>
<tr>
<td><strong>Shape &amp; margins</strong></td>
<td>Round or oval with well-defined margins</td>
<td>Irregular shape and margins. Invasion to surrounding tissues</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Composition</strong></td>
<td>Homogenous</td>
<td>Heterogeneous (hemorrhage, necrosis)</td>
<td>Heterogeneous (necrosis)</td>
<td>Heterogeneous (hemorrhage, necrosis)</td>
</tr>
<tr>
<td><strong>CT Unenhanced attenuation</strong></td>
<td>≤10 HU (or &gt;10 HU for lipid-poor adenomas)</td>
<td>&gt;10 HU</td>
<td>&gt;10 HU</td>
<td>&gt;10 HU</td>
</tr>
<tr>
<td><strong>CT Percent Washout (PW)</strong></td>
<td>APW &gt;60%, RPW&gt;40%</td>
<td>APW&lt;60%, RPW&lt;40%</td>
<td>APW&lt;60%, RPW&lt;40%</td>
<td>APW&lt;60%, RPW&lt;40%</td>
</tr>
<tr>
<td><strong>MRI - CSI (out-of phase)</strong></td>
<td>Signal loss (except in lipid-poor adenomas)</td>
<td>No change in signal intensity</td>
<td>No change in signal intensity</td>
<td>No change in signal intensity</td>
</tr>
<tr>
<td><strong>FDG uptake (PET)</strong></td>
<td>Low (some can have low to moderate uptake)</td>
<td>High</td>
<td>Low (malignant pheochromocytomas show high uptake)</td>
<td>High</td>
</tr>
<tr>
<td><strong>NP-59 uptake</strong></td>
<td>Present</td>
<td>Absent (except in some secreting tumors)</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

ACC: Adrenocortical carcinoma; HU: Hounsfield Units; APW: Absolute PW; RPW: Relative PW; CSI: Chemical-shift Imaging; FDG: fluoro-deoxyglucose; NP-59: 131I-6-b-iodomethyl-norcholesterol
The purpose of biochemical testing is to determine the functionality of adrenal masses. The idea that all functional nodules should come out is not universally true.
Biochemistry

- The history is of course very important in the evaluation of the adrenal nodule.
  - History is our best opportunity to reduce overall cost and risk to the patient.
  - Identifying those patients who look floridly Cushingoid or those who have resistant hypertension and require multiple drugs to control their blood pressure or have classic symptoms of pheochromocytoma can assist in determining the pretest probability of your lab testing.
  - It is important to note that we are talking about “incidental” masses and these patients may be completely asymptomatic and have no clear signs of disease and thus be sub or pre clinical.
Biochemistry

The initial clinical/biochemical work up of an adrenal nodule:

- Plasma Aldosterone Concentration (PAC)
- Plasma Renin Activity
- Urine Free Cortisol
- Urine Catecholamines and Metanephrines or Plasma Fractionated Metanephrines
Aldosterone Secreting Adenomas

- One percent of adrenal incidentalomas are associated with autonomous production of aldosterone.
- Drug resistance and refractory hypertension (need for >3 antihypertensive agents) are common hallmarks of primary aldosteronism.
- Spontaneous hypokalemia (serum potassium <3.5 mEq/L) or severe (<3 mEq/L) diuretic-induced hypokalemia.
- Most patients with primary aldosteronism do not have hypokalemia.
- Most forms of primary hyperaldosteronism are of the multinodular type and do not require surgery.
- In addition select patient populations aldosterone secreting adenomas do not require surgery.
Aldosterone Secreting Adenomas

- Determining the ratio (A/R) of PAC (ng/dL) to PRA (ng/mL per hour) has become the accepted screening modality for primary aldosteronism.
  - An absolute value of 20 ng/dL increases the sensitivity of the A/R.
  - Patient must stop aldactone or eplerenone before testing.
Aldosterone Secreting Adenomas

Screening

- In the presence of an ARB, ACEI or diuretics the Plasma Renin activity should generally be elevated or upper limit of normal.
- If you see a low renin in patients taking an ARB, ACEI or thiazide diuretic this should heighten your suspicion for autonomous aldosterone secretion.
- A/R of over 20 is highly sensitive to the presence of primary aldosteronism.
- Many texts use an A/R of 15 for the cut off of the screening test.
Aldosterone Secreting Adenomas

- The A/R is most sensitive when blood samples are collected in the morning, after patients have been out of bed for at least 2 hours and have been seated for 5 to 15 minutes.
Cortisol Secreting Adenomas

- Benign Cortisol Secreting Nodules
  - It is important here to pay attention to the imaging guidelines in patients with adrenal nodules and any evidence of Cushing’s syndrome or rapid onset of hirsutism or virilization.
  - A significant portion of malignant adrenal cortical carcinoma secrete cortisol, androgens or both.
Cortisol Secreting Adenomas

- Screening for Cushing’s syndrome in patients with adrenal adenomas.
  - The clinical presentation guides us towards our initial testing.
  - The 1 mg dexamethasone test is the test of choice in patients who present with an adrenal mass and have a low clinical suspicion for Cushings.
    - Give 1 mg dexamethasone between 10 PM and 11 PM followed by an 8 AM cortisol level.
    - If the cortisol is over 5 mg/dL then move forward with further testing to confirm Cushings.
Cortisol Secreting Adenomas

- For patients who have clinical evidence of Cushing’s the standard guidelines for the evaluation of Cushing’s syndrome apply
  - Start with a 24 hour urine cortisol
  - If positive then move to another screening test such as the 1 mg dexamethasone test.
Adrenocortical Carcinoma

- It is important to remember that ACC can present exactly the same way as subclinical Cushing’s due to a benign adenoma.

- CT imaging characteristics are very important in the evaluation of ACC
  - An incidentaloma with >10 HU attenuation on non-contrast CT is concerning for an ACC,
  - However an attenuation >30 HU is very concerning.
  - Important to remember that a pheochromocytoma can be as dense as ACC.
Two-thirds of all ACCs are hormonally active and tend to manifest with hypercortisolism and virilization (and, rarely, aldosteronism and feminization).

In the past many patients with ACC presented with Cushing’s syndrome but in our overweight society subclinical or even overt Cushing’s is becoming more difficult to discern from severe obesity.

Smaller ones can be subclinical.
The presence of a pheochromocytoma should be suspected in patients with severe hypertension, tachycardia, palpitations, cardiac arrhythmias, anxiety attacks, weight loss, or sweating.

About 15% of patients with a pheochromocytoma have no history of hypertension.
Pheochromocytoma

- A 24-hour urine total metanephrine level above 1,800 µg in the appropriate clinical setting is almost always diagnostic for a pheochromocytoma.
- No value less than 2x the upper limit of normal should be considered diagnostic and should always add suspicion and be repeated after 4-6 months.
Pheochromocytoma

- A plasma metanephrine level exceeding 3 to 4 times normal is highly diagnostic for a pheochromocytoma.

- Measurement of plasma free metanephrines and normetanephrines has the highest sensitivity (97% to 100%) and specificity (85% to 89%) and appears to be the best initial test for screening patients for pheochromocytoma.

- The plasma metanephrines are quickly over taking the 24 hour urine as the test of choice by endocrinologist.
Pheochromocytoma

- Test interference
  - However there are a number of medicines known to interfere with the measurements of both urine and plasma metanephrine levels.
  - Tricyclic antidepressants
  - Cyclobenzaprine
  - Decongestants
  - Amphetamines
  - Reserpine
  - Phenoxybenzamine

- It is very important that you screen your patients specifically for these drugs.
**Metastatic Lesions**

- **Metastatic Lesions to the Adrenal Gland**
  - Two pooled analyses of international studies reported a 2.1% to 2.5% prevalence of metastatic lesions among incidentalomas.
  - Lung, breast, stomach, and kidney cancers and melanomas and lymphomas most commonly metastasize to the adrenal glands.
Metastatic Lesions

The distinction between a metastatic lesion and ACC is simply a known history of an existing primary malignancy and sometimes by the clinical presence of symptomatic Cushings.
Metastatic Lesions

The only adrenal mass in which it is appropriate to do a CT guided adrenal biopsy is the highly suspected metastatic lesion and only if it will change the management of the patients primary cancer.

- No biopsy should occur until the patient has been biochemically screened for pheochromocytoma and the probability of ACC is very low.
- Pheo crisis in the former and local/regional spread of the latter is well documented.
Myelolipoma

- Myelolipoma is a rare, benign neoplasm that predominantly occurs in the adrenal gland and is composed of mature adipose tissue and scattered islands of hematopoietic elements.
- Usually small and asymptomatic, there are some cases of adrenal myelolipoma that cause symptoms such as chronic pain.
- Can also be quite large and easily present as adrenal masses over 4 cm.
- Can present with chronic abdominal or flank pain especially if CT shows a multidense gland suggestive of previous hemorrhage.
Myelolipoma

- Imaging

- CT scan of Myelolipomas are generally -20 to -30 Hounsfield units thus much less dense than most adenomas.

- They are usually identified by the radiologist and reported as such.
  - However, thorough evaluation of adrenal mass is still warranted.
Myelolipoma

- Are the exception to the 4 cm rule.
  - If asymptomatic surgery can be avoided if the patient is asymptomatic.
  - Once they reach 6 cm it generally becomes necessary to remove due to risk of painful and sometimes life threatening hemorrhage.
Surveillance

- Patients with adrenal incidentalomas who do not fulfill the criteria for surgical resection need to have radiographic reevaluation at 3 to 6 months and then annually for 1 to 2 years.
So our patient presents with a presumed Pheochromocytoma.

What is the next step in the management of this patient given the standard guidelines recommendations?
Roundup

**What we know so far**
- CT Abdomen (3/2016): 1.3 cm left adrenal mass -16 HU on pre-contrast images.
- Uses high dose Amitriptyline
- Rash but no flushing
- Plasma Metanephrine 0.51 (0-0.49)
- Plasma Normetanephrine 1.12 (0-0.89)

**Urine**
- Epinephrine 7 (0-12)
- Norepinephrine 228 (16-71)
- Metanephrine 270 (62-207)
- Normetanephrine 753 (125-510)
Roundup

- Stop the Amitriptyline and repeat labs
  - Plasma Metanephrine 0.39 (0-0.49)
  - Plasma Normetanephrine 0.7 (0-0.89)
- Urine
  - Epinephrine 8 (0-12)
  - Norepinephrine 48 (16-71)
  - Metanephrine 212 (62-207)
  - Normetanephrine 580 (125-510)
Patient is currently under surveillance to make sure the remainder of his labs normalize.
References

- Boland GW, Blake MA, Holalkere NS, Hahn PF. PET/CT for the characterization of adrenal masses in patients with cancer: qualitative versus quantitative accuracy in 150 consecutive patients. AJR American journal of roentgenology 2009; 192:956-962


References

