Pheochromocytoma and paraganglioma

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Case presentation

- 54 yo Caucasian male with HTN and paroxysmal symptoms for >20 years
- Episodes of hot flashes, sweating, headache, palpitations and facial flushing. Hard to control HTN. Several MDs considered pheo but “nothing was done”
- PMH: psoriasis. Obesity
- BP 131/76, HR 77, BMI 38.
- 24-hour urine normetanephrine 749 (<676) metanephrine 148 (<315)
- Abdominal CT: 1.1-cm left adrenal mass consistent with adenoma
Case presentation

• **Endocrinology note**: “although U metanephrines not dramatically elevated, they're still elevated, and in conjunction w/ current sx, clinical suspicion for pheo is high. would recommend surgical eval for excision/biopsy”

• **General surgery note**: “known 11 mm L adrenal mass c/w pheochromocytoma”, “Risks and benefits of laparoscopic adrenalectomy discussed”

• **What would you recommend?**
Pheo and paraganglioma

3 topics to be discussed:

1. Natural history and presentation
2. Diagnosis
3. Preoperative preparation
Pheo and para basics

• Tumor of adrenal medulla (pheochromocytoma, ~90%) or extra-adrenal (paraganglioma, ~10%)

• Most pheos are functional; 50% of paras in abdomen and pelvis are functional; most paras in head/neck and mediastinum are NOT functional.

• A rare cause of hypertension (0.2-2%)

• Most are curable by surgical removal
# Location of Paraganglioma

<table>
<thead>
<tr>
<th>Location</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasympathetic (nonsecretory)</td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>95</td>
</tr>
<tr>
<td>Catecholamine secreting</td>
<td></td>
</tr>
<tr>
<td>Abdominal para-aortic</td>
<td>75</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>10</td>
</tr>
<tr>
<td>Thorax</td>
<td>10</td>
</tr>
<tr>
<td>Head and neck</td>
<td>3</td>
</tr>
<tr>
<td>Pelvis</td>
<td>2</td>
</tr>
</tbody>
</table>

Pheo- natural history

• Classical literature  Bravo *Endo Rev* 24:539, 2003
  – Hypertension  90%
  – Headache  80%
  – Palpitation  64%
  – Sweating  57%

  – 33% presented with hypertension
  – 40% presented with incidental adrenal mass
PHEO: Revised *Rule of 10s*

**Then**
- 10% extra-adrenal
- 10% in children
- 10% bilateral
- 10% recur
- 10% malignant
- 10% familial
- 10% *incidentalomas*

**Now**
- 70% *incidentalomas*!
- 30% familial
  (germ line mutations)
- 12% unexplained HF
  (Takotsubo), ACS, or VT
  without paroxysmal hypertension
## Small vs. larger pheos

<table>
<thead>
<tr>
<th></th>
<th>Small (≤3 cm)</th>
<th>Larger (&gt;3 cm)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n )</td>
<td>24</td>
<td>51</td>
<td>NA</td>
</tr>
<tr>
<td>1995-2002/2003-2011, ( n )</td>
<td>4/20</td>
<td>22/29</td>
<td>0.037</td>
</tr>
<tr>
<td>Age, average (range), year</td>
<td>53.8 (16-82)</td>
<td>49.8 (10-85)</td>
<td>0.354</td>
</tr>
<tr>
<td>Sex, f/m, ( n )</td>
<td>16/8</td>
<td>29/22</td>
<td>0.459</td>
</tr>
<tr>
<td>Presentations, ( n )</td>
<td>13/9/2</td>
<td>21/10/20</td>
<td>0.328/0.153/0.007</td>
</tr>
<tr>
<td>incidental/hypertension/others,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac presentations, ( n )</td>
<td>0</td>
<td>9</td>
<td>0.050</td>
</tr>
<tr>
<td>QTc, ms (range)</td>
<td>433 (394-495)</td>
<td>454 (397-521)</td>
<td>0.082</td>
</tr>
<tr>
<td>Hypertensive crisis during</td>
<td>4</td>
<td>5</td>
<td>0.455</td>
</tr>
<tr>
<td>unrelated procedures, ( n )</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Do small pheos cause HTN?

• Many people have HTN
• Some of them may have a small pheo
• Does the small pheo cause, contribute, or have nothing to do with HTN?
# Small vs. larger pheos: effects of surgery

<table>
<thead>
<tr>
<th></th>
<th>Small (≤3 cm)</th>
<th>Larger (&gt;3 cm)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>27</td>
<td>NA</td>
</tr>
<tr>
<td>Age, average (range), year</td>
<td>51 (16-82)</td>
<td>51 (10-85)</td>
<td>0.946</td>
</tr>
<tr>
<td>Sex, F/M, n</td>
<td>12/8</td>
<td>14/13</td>
<td>0.767</td>
</tr>
<tr>
<td>Preoperative hypertension, yes/no, n (%)</td>
<td>13/7 (65)</td>
<td>22/5 (82)</td>
<td>0.311</td>
</tr>
<tr>
<td>Hypertension, improved/not improved, n (%)</td>
<td>3/10 (23)</td>
<td>14/8 (64)</td>
<td>0.035</td>
</tr>
<tr>
<td>Other symptoms, improved/not improved, n (%)</td>
<td>5/5 (50)</td>
<td>9/3 (75)</td>
<td>0.377</td>
</tr>
</tbody>
</table>
Summary on small pheos

- More common now
- Mostly presenting as adrenal mass
- May cause hypertension in some patients
- Can cause hypertensive crisis during unrelated procedures
- Should be removed if possible
The growth speed of sporadic pheos

Yu & Phillips *Clinical Endocrinology* 77:331, 2012
Larger pheos

- Classically described
- Various presentations
  - Hypertension, headache, palpitations, sweating, flushing, pallor, nervousness, fatigue, nausea/vomiting, chest/ab pain, fainting, paresthesia, constipation, visual disturbances, hyperglycemia, thyroid swelling,…
- Asymptomatic to dramatic
- **Cardiac presentations** are the most clinically important
## Larger pheos: silent vs. symptomatic

<table>
<thead>
<tr>
<th></th>
<th>Clinically inapparent</th>
<th>Symptomatic</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>24</td>
<td>NA</td>
</tr>
<tr>
<td>Age, average (range), yr</td>
<td>61 (35-85)</td>
<td>44 (22-73)</td>
<td>0.001</td>
</tr>
<tr>
<td>Biochemical marker levels, average (range), fold</td>
<td>7.6 (1.0-21.9)</td>
<td>24.2 (1-89.6)</td>
<td>0.029</td>
</tr>
<tr>
<td>Tumor size, average (range), cm</td>
<td>6.3 (3.3-15.0)</td>
<td>6.4 (3.5-15.1)</td>
<td>0.924</td>
</tr>
<tr>
<td>QTc, average (range), n*</td>
<td>435 (397-501)</td>
<td>464 (418-521)</td>
<td>0.019</td>
</tr>
<tr>
<td>Intraoperative blood pressure fluctuation, yes/no, n*</td>
<td>2/13</td>
<td>5/18</td>
<td>0.681</td>
</tr>
<tr>
<td>Postoperative blood pressure control, Improved/unchanged, n*</td>
<td>2/9</td>
<td>13/0</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Yu J *Endocrinol Invest* 35:349, 2012
Pheo cardiac presentations

• Subclinical and clinical cardiac abnormalities are common in Pheo
• 12% of Pheo present with cardiac complications
• Larger tumor and higher marker levels are associated with higher cardiac risks
• Abnormal ECG findings are ST-T changes and QT prolongation
• QTc is correlated with norepinephrine or normetanephrine levels
• Left ventricular wall motion can be abnormal in patients with longer QTc

The natural history of pheo

Genetic disposition

Normal adrenal medulla

Oncogene activation
TSG inactivation

Adrenal medulla hyperplasia

Additional mutations

Small pheo

Hypertension

Large pheo

Pheo crisis

Pheo crisis
CHF, MI, Shock…

Hypertension
Paroxysm
Others
When to Screen for PHEO/Paraganglioma?

Hyperadrenergic spells
Resistant hypertension
Family history of pheochromocytoma or paraganglioma
Familial syndrome (e.g., MEN2, VHL)
Hypertensive response to anesthesia
Onset of hypertension before the age of 20 y
Hypertension with dilated cardiomyopathy
Adrenal incidentaloma
New onset of cardiomyopathy without a clear etiology
Pheo diagnosis

• Often challenging in contemporary practice
• Misdiagnoses are common
  – Over-diagnosis=23%
  – Under-diagnosis=25%
• Clinical, biochemical, and imaging are all needed
• Biopsy is contraindicated in most cases

Clinical Suspicion
based on natural history

• Pheo is very likely:
  – Young patients with bilateral adrenal mass
  – Idiopathic cardiomyopathy with adrenal mass
Clinical Suspicion based on natural history

• Pheo still needs to be ruled out:
  – Incidental adrenal mass without HTN
  – Adrenal mass without growth in several years
  – Small adrenal mass
  – Resistant HTN
  – HTN with paroxysmal symptoms
Clinical Suspicion based on natural history

• Pheo is **very unlikely:**
  – No tumors in chest, abdomen, or pelvis
  – Adrenal hypertrophy without mass
Pheo- biochemical diagnosis

• Biochemical diagnosis
  – Critical for Pheo diagnosis
  – Best tests: plasma fractionated metanephrines
  – 2nd bests: 24-hr urine metanephrines
  – Chromogranin A and NSE have unique value in small tumors
  – Catecholamines have unique use in dopamine-dominant pheo

• False positive and false negative results are quite common
Plasma Metanephrines

**COMT**
- Enriched in adrenal chromaffin cells
- Converts NE & EPI to o-methyl derivatives:
  - normetanephrine (NMN)
  - metanephrine (NM)

Continuous non-vesicular leak into plasma
Test results - interference

- Body posture and stress during blood draw
- Age: older people have higher normetanephrine
- Season: normetanephrine 40% higher in winter
- Medications:
  - Physiological: phenoxybenzamine, tricyclics, MAO inhibitors
  - a1 blockers doxazosin, terazosin, prazosin: OK
  - b blockers atenolol, metoprolol, propranolol, combined a/b
    blocker labetolol: OK for plasma, interfere with urine
- Technical: assay dependent.
  - Buspirone, acetaminophen, pseudoephedrine

False results

• False negative:
  – Rare clinical situations
  – Small or cystic pheo

• False positive:
  – Much more common
  – A larger problem for physicians and patients
  – Can result in adrenalectomy if patient has an adrenal mass
  – Clinical situations are diverse and often case-by-case

Yu & Wei *ECED* 118:577, 2010
Pheo imaging

• CT and MRI are both useful. MRI slightly better
  – Medium density on CT (HU >10)
  – Brighter on T2 on MRI
  – No loss of signal on out-of-phase MRI imaging
  – Enhancing upon contrast
  – Contrast retaining (<50% wash out)
Classical pheo images

Before contrast 1 min after 10 min after

CT

T1 T1 post gadolinium

MRI
pheo imaging- nuances

• High metanephrines suggest larger pheos
• Small pheos (<1-2 cm) may have normal metanephrines
• Small ones have more classical appearance
• Larger ones can have cysts, hemorrhage, or degeneration
• Atypical findings cannot exclude pheo
• Typical findings are suggestive but not specific
  • Adrenocortical carcinoma, mets, pheo, paraganglioma, schwannoma, ganglioneuroma, ganglioneuroblastoma, neuroblastoma,...
## Functional imaging

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIBG</td>
<td>77-90%</td>
<td>95-100%</td>
</tr>
<tr>
<td>Cedars</td>
<td>73%</td>
<td>69-90%</td>
</tr>
<tr>
<td>Octreotide</td>
<td>30-60%</td>
<td>?</td>
</tr>
<tr>
<td>FDG PET</td>
<td>76-92%</td>
<td>?</td>
</tr>
</tbody>
</table>

*Lev Endo Pract 16:398, 2010*
Integrated diagnostic decision

Clinical suspicion

- **Metanephrines**
  - Normal
  - Borderline
  - High

Ruled out

Repeat

CT/MRI

Adrenal mass

- **Metanephrines**
  - Abnormal
  - Normal

Individual decision

Ruled out

Clonidine

- Pass
- Fail

Borderline

High
Pre-operative management

• Preop prep somewhat controversial, not evidence-based: overall need; specific regimen may vary
• Endo Society: at least alpha blockade
• 3 goals:
  – BP control (traditional)
  – Fluid repletion (traditional)
  – Cardiac function recovery (probably the real goal)
• 3 components:
  – Vasodilation: alpha blocker or calcium channel blocker
  – Fluid: encourage salt intake
  – Duration: ideally >2 weeks
Back to the case…

• Pt is "not sure" if he wants surgery.
• Did extensive search on internet about diagnosis and treatment of pheo.
• He sought second opinion
My Opinion

“Though patient has elevated urinary normetanephrine, the elevation is only mild.

In the setting of this mild elevation with small size on CT (11mm) despite symptoms for >20 yrs (expect pheo to grow if present >20yrs), CT c/w adenoma, **pheo is unlikely**.

Patient may have **adrenal incidentaloma**. to fully work-up and r/o pheo, patient may consider clonidine suppression test.”
Summary

• The natural history of pheochromocytoma is the foundation of diagnosis and management strategies
• Pheochromocytoma diagnosis needs to integrate clinical, biochemical, and imaging data
• Preoperative preparation is needed to reduce perioperative cardiovascular risk