“51 Year Old Female with Palpitations”
ENDORAMA:
51 Year Old Female with Palpitations

Monika Darji
September 12th, 2019
Objectives

• Discuss the workup and diagnosis of pheochromocytoma
• Discuss the role of genetic testing in pheochromocytoma
• Review the criteria for diagnosis of malignant pheochromocytoma
Chief Complaint

51 year old female presents with palpitations
HPI

• Presents with palpitations for 1 year
  • Progressively getting worse over last several months
  • Lasts minutes to hours, occurs multiple times per day
  • Associated with nausea, anxiety, headaches, diaphoresis
  • Noticed it was associated with blood pressure spikes
• No previous history of palpitations
• No known cardiac history
Review of Systems

- Constitutional: +fatigue, diaphoresis; No fever, chills, activity change
- HEENT: +headaches; No visual disturbance, hearing loss, congestion, sore throat, neck pain
- Resp: +dyspnea on exertion; No cough
- CV: +palpitations; No CP, LE edema
- GI: +nausea; No nausea or vomiting. No abdominal pain, d/c, or blood in stool
- MSK: +myalgias
- Skin: No rashes or ulcers.
- Neuro: No lightheadedness, seizures, syncope
- Endo: No heat/cold intolerance. No hair/skin changes noted
- Heme: No adenopathy
- Psych: +anxiety, depression
Additional history

- Past Medical History: polymyositis, hypertension, asthma, depression
- Past Surgical History: none
- Family History: mother has asthma, father had lung cancer
- Social History: smokes half a pack of cigarettes per day for the last 20 years, social drinker, denies illicit drug use
Additional history

• Meds: prednisone 15mg, azathioprine 200mg, amlodipine 5mg, fluoxetine 20mg, albuterol

• Allergies: NKDA
Physical Exam

- Vitals: 139 kg, BMI 42, Temp 97.5, HR 105, RR 18, BP 108/78, SpO2 99%
- General: Obese; No apparent distress. Appears stated age.
- HEENT: Normocephalic. PERRL, EOMI. No pharyngeal erythema.
- Neck: No neck tenderness. No thyromegaly or thyroid nodules appreciated.
- Cardiovascular: Tachycardic. Regular rhythm. Trace peripheral edema.
- Pulmonary/Chest: Clear to auscultation bilaterally.
- Gastrointestinal: Soft, non-tender, non-distended. No rebound or guarding.
- Musculoskeletal: Normal bulk and tone, no major deformities.
- Neurological: Alert & oriented, CN 2-12 intact.
- Skin: No rashes or bruises.
- Psychiatric: Anxious. Normal thought content, appropriate.
Labs

Anion gap 14

- Total protein: 8.1
- Albumin: 4.5
- Total bilirubin: 0.8
- Alkaline phosphatase: 86
- ALT: 26
- AST: 12
- Ca: 9.1
- TSH: 1.74
Differential diagnosis

- Pheochromocytoma
- Hyperthyroidism
- Carcinoid
- Insulinoma
- Paroxysmal supraventricular tachycardia
- Ischemic heart disease
- Anxiety disorder
- Substance use or withdrawal
## Workup

<table>
<thead>
<tr>
<th>Lab</th>
<th>Value</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma normetanephrine</td>
<td>4.4 nmol/L</td>
<td>&lt; 0.90 nmol/L</td>
</tr>
<tr>
<td>Plasma metanephrine</td>
<td>&lt; 0.20 nmol/L</td>
<td>&lt; 0.50 nmol/L</td>
</tr>
<tr>
<td>Urine norepinephrine</td>
<td>1,111 mcg/24hr</td>
<td>15 – 80 mcg/24hr</td>
</tr>
<tr>
<td>Urine epinephrine</td>
<td>16 mcg/24hr</td>
<td>&lt; 21 mcg/24hr</td>
</tr>
<tr>
<td>Urine dopamine</td>
<td>239 mcg/24hr</td>
<td>65 – 400 mcg/24hr</td>
</tr>
<tr>
<td>Urine total metanephrines</td>
<td>3,797 mcg/24hr</td>
<td>164 – 588 (normotensive)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 1300 (hypertensive)</td>
</tr>
<tr>
<td>Urine normetanephrines</td>
<td>3,614 mcg/24hr</td>
<td>128 – 484 (normotensive)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 900 (hypertensive)</td>
</tr>
<tr>
<td>Urine metanephrines</td>
<td>183 mcg/24hr</td>
<td>30 – 180 (normotensive)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 400 (hypertensive)</td>
</tr>
</tbody>
</table>
Cardiac workup

- Event monitor
  - Sinus rhythm with episodes of sinus tachycardia and junctional rhythm during which the patient was symptomatic
- 2D echocardiogram
  - LV EF 44%
  - Mild left ventricular hypertrophy

- MRI cardiac stress
  - No perfusion defects or ischemia
  - No prior myocardial infarction
  - Concern for early myocarditis or diffuse interstitial fibrosis

- Cardiac PET
  - FDG uptake in the inferior wall, inferolateral wall, and apex of the LV, c/w inflammatory change in the myocardium
Cardiology appointment

- Heart failure thought to be 2/2 inflammatory myopathy, unlikely ischemic given normal stress perfusion
- Beta blocker held
- Started on lasix 20mg daily, doxazosin 1mg QHS
- ACE-I held given borderline BPs
- RHC with biopsy
Imaging

- CT abdomen/pelvis
  - Enhancing right adrenal nodular lesion measuring 3.1 x 2.3 cm
    - Absolute washout of 73%, relative washout 40%
    - High absolute attenuation within portal venous phase
  - Left adrenal is normal in appearance
Pheochromocytoma and Paragangliomas (PPGL)

- Pheochromocytoma – tumor arising from adrenal medullary chromaffin cells that commonly produce one of more catecholamines (80 - 85% chromaffin cell tumors)
- Paraganglioma – tumor arising from extra-adrenal chromaffin cells of the sympathetic paravertebral ganglia of thorax, abdomen, and pelvis (15- 20 % chromaffin cell tumors)
  - Can also arise from parasympathetic ganglia along glossopharyngeal and vagal nerves in neck and at base of skull
PPGL

• Prevalence in patients with hypertension estimated to be 0.2-0.6%
• In patients with incidentally discovered adrenal masses on imaging, estimated 5% have pheochromocytomas
• At least 1/3 of patients with PPGLs have disease causing germline mutations
  • Most common in the fourth to fifth decade of life
  • Equally common in men and women
Clinical Presentation

• Symptoms present in approximately 50% of patients
• Classic triad – episodic headache, diaphoresis, and tachycardia
• Hypertension can be sustained or paroxysmal – most common sign
• Other symptoms include palpitations, tremor, generalized weakness, dyspnea
  • Less common symptoms/signs - orthostatic hypotension, cardiomyopathy
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Paroxysmal N=37</th>
<th>Persistent N=39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches (severe)</td>
<td>92%</td>
<td>72%</td>
</tr>
<tr>
<td>Excessive sweating (generalized)</td>
<td>65%</td>
<td>69%</td>
</tr>
<tr>
<td>Palpitations with or without tachycardia</td>
<td>73%</td>
<td>51%</td>
</tr>
<tr>
<td>Anxiety, nervousness, fear of impending death, or panic</td>
<td>60%</td>
<td>28%</td>
</tr>
<tr>
<td>Tremulousness</td>
<td>51%</td>
<td>26%</td>
</tr>
<tr>
<td>Pain in chest, abdomen (usually epigastric), lumbar regions, lower abdomen, or groin</td>
<td>48%</td>
<td>28%</td>
</tr>
<tr>
<td>Nausea with or without vomiting</td>
<td>43%</td>
<td>26%</td>
</tr>
<tr>
<td>Weakness, fatigue, prostration</td>
<td>38%</td>
<td>15%</td>
</tr>
<tr>
<td>Weight loss (severe)</td>
<td>14%</td>
<td>15%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11%</td>
<td>18%</td>
</tr>
<tr>
<td>Warmth or heat intolerance</td>
<td>13%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Noteworthy are painless hematuria, urinary frequency, nocturia, and tenesmus in pheochromocytoma of the urinary bladder.
Indications for testing

- Patients presenting with the classic triad of symptoms or hyperadrenergic episodes
- Early onset of hypertension or resistant hypertension
- Familial syndrome like MEN2, VHL, NF1
- Family history of pheochromocytoma
- Incidental adrenal mass with or without hypertension
- Idiopathic dilated cardiomyopathy
Interfering medications

**Medications that may increase measured levels of catecholamines and metanephrines**

- Tricyclic antidepressants
- Levodopa
- Drugs containing adrenergic receptor agonists (eg, decongestants)
- Amphetamines
- Buspirone and most psychoactive agents
- Prochlorperazine
- Reserpine
- Withdrawal from clonidine and other drugs
- Ethanol
Initial Testing

- 24-hour urinary fractionated metanephrines or plasma fractionated metanephrines (drawn supine with an indwelling cannula for 30 minutes)
- Plasma fractionated metanephrines
  - Sensitivity of 96 to 100 percent, specificity of 85 to 89 percent
  - Can consider as a first-line test for pheochromocytoma for patients with high suspicion of pheochromocytoma
    - Family history of pheochromocytoma
    - Hereditary syndrome
    - Past history of resected pheochromocytoma
Table 3. Sensitivities and Specificities of Biochemical Tests for Diagnosis of Hereditary and Sporadic Pheochromocytoma*

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity, %†</th>
<th>Specificity, %‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hereditary</td>
<td>Sporadic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free metanephrines</td>
<td>97 (74/76)</td>
<td>99 (137/138)</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>69 (52/75)</td>
<td>92 (126/137)</td>
</tr>
<tr>
<td>Urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractionated metanephrines</td>
<td>96 (26/27)</td>
<td>97 (76/78)</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>79 (54/68)</td>
<td>91 (97/107)</td>
</tr>
<tr>
<td>Total metanephrines</td>
<td>60 (27/45)</td>
<td>88 (61/69)</td>
</tr>
<tr>
<td>Vanillymandelic acid</td>
<td>46 (30/65)</td>
<td>77 (66/86)</td>
</tr>
</tbody>
</table>

*The reference limits used to calculate sensitivity and specificity are presented in Table 2.†For free plasma metanephrines or urinary fractionated metanephrines, sensitivity was calculated from patients with pheochromocytoma and false-negative test results for both normetanephrine and metanephrine. For plasma and urine catecholamines, sensitivity was calculated from patients with both false-negative test results for nonepinephrine and epinephrine. Numbers in parentheses indicate true positive over true positive plus false-negative.‡For free plasma metanephrines or urinary fractionated metanephrines, specificity was calculated from patients without pheochromocytoma and with false-positive test results for either normetanephrine or metanephrine. For plasma and urine catecholamines, specificity was calculated from patients without pheochromocytoma and with false-positive test results for either nonepinephrine or epinephrine. Numbers in parentheses indicate true negative over true negative plus false-positive.
Evaluation and treatment of catecholamine-producing tumors

- Suspected catecholamine-secreting tumor
  - Discontinue interfering medications
    - Case detection testing with either:
      - 24-hour urine fractionated metanephrines and catecholamines, or
      - Plasma fractionated metanephrines drawn from indwelling cannula following 30 minutes of supine rest
    - Normal
      - Recheck during a spell
    - Normal: Twofold elevation above upper limit of normal in urine catecholamines or elevated urine metanephrines (Nmet >900 mcg per 24 hours or Met >400 mcg per 24 hours) or "significant increase" in fractionated plasma metanephrines

- Investigate other causes of spells
  - Localize:
    - Adrenal/abdominal MRI or CT scan
      - Typical adrenal or para-aortic mass:
        - Iobenguane I-123 scan if:
          - >10 cm adrenal mass
          - Paraganglioma
        - Reassess the diagnosis
          - Consider:
            - Iobenguane I-123 scan
            - Whole body MRI scan
            - 68-Ga DOTATATE or FDG PET scan
          - Tumor found
            - Consider genetic testing
              - Preoperative alpha- and beta-adrenergic blockade
            - Surgical resection if anatomically feasible

Uptodate 2019
Imaging

- **CT abdomen/pelvis**
  - First choice imaging modality
  - Increased attenuation on nonenhanced CT (>20 Hounsfield units)
  - Increased mass vascularity
  - Delay in contrast medium washout

- **MRI abdomen/pelvis**
  - High signal intensity on T2-weighted MRI

- **Iobenguane I-123**
  - >10 cm adrenal pheochromocytomas
  - Paragangliomas

- **FDG-PET**
  - More sensitive than I-123 or CT/MRI for detection of metastatic disease
Genetic testing

• At least one-third of all patients with PPGLs have disease-causing germline mutations
  • More likely to be bilateral adrenal pheochromocytomas or paragangliomas

• Familial disorders associated with pheochromocytoma:
  • Von Hippel-Lindau syndrome (VHL) – 10-20%
  • Multiple endocrine neoplasia type 2 (MEN2) – 30-50%
  • Neurofibromatosis type 1 (NF1) – 0.1 to 5.7%

• Most cases of familial paraganglioma are caused by mutations in the succinate dehydrogenase (SDH) subunit genes
Genetic Testing

• Guidelines recommend shared decision making for genetic testing

• Consider genetic testing for patients with:
  • Paraganglioma
  • Bilateral adrenal pheochromocytoma
  • Unilateral adrenal pheochromocytoma with family history of pheochromocytoma or diagnosed at young age (<35yo)
  • Clinical features suggestive of hereditary syndrome
PPGL diagnosis

Syndromic presentation → Targeted genetic testing

Metastatic

SDHB → SDHD, SDHC, VHL, MAX

Nonmetastatic

Skull base and neck → SDHD, SDHB, SDHC

Extra-adrenal

Dopaminergic → SDHB, SDHD, SDHC

Noradrenergic → SDHB, SDHD, SDHC, VHL, MAX

Adrenal

Dopaminergic → SDHD, SDHB, SDHC

Noradrenergic → VHL → SDHD, SDHB, SDHC, MAX

Adrenergic → RET → TMEM127, MAX
Back to our patient

• Seen by endocrine surgery in clinic and referred to anesthesiology for pre-operative evaluation and optimization of alpha blockade
• Symptoms improved since stopping beta-blocker and starting doxazosin – reported decrease in the number and length of “attacks”
• Underwent laparoscopic right adrenalectomy
• Postoperative course was complicated by hypotension requiring a brief ICU stay and vasopressors
• Discharged to subacute rehab
Pre-op management

Table 9. Presurgical Medical Preparation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Time</th>
<th>Starting Dose</th>
<th>Final Dose&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation 1</td>
<td>10–14 d before surgery</td>
<td>10 mg b.i.d.</td>
<td>1 mg/kg/d</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>10–14 d before surgery</td>
<td>2 mg/d</td>
<td>32 mg/d</td>
</tr>
<tr>
<td>or Doxazosine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preparation 2</td>
<td>As add-on to preparation 1 when needed</td>
<td>30 mg/d</td>
<td>60 mg/d</td>
</tr>
<tr>
<td>Nifedipine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>As add-on to preparation 1 when needed</td>
<td>5 mg/d</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>or Amlodipine&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preparation 3</td>
<td>After at least 3–4 d of preparation 1</td>
<td>20 mg t.i.d.</td>
<td>40 mg t.i.d.</td>
</tr>
<tr>
<td>Propranolol</td>
<td>After at least 3–4 d of preparation 1</td>
<td>25 mg/d</td>
<td>50 mg/d</td>
</tr>
<tr>
<td>or Atenolol</td>
<td></td>
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</tbody>
</table>

Abbreviations: b.i.d., twice daily; t.i.d., three times daily.

<sup>a</sup> Add when blood pressure cannot be controlled by α-adrenoceptor blockade (preparation 1).

<sup>b</sup> Higher doses usually unnecessary.
Post op visit

• 1 month post op visit – patient was feeling well, symptoms resolved

<table>
<thead>
<tr>
<th>Lab</th>
<th>Value</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma dopamine</td>
<td>&lt; 25 pg/mL</td>
<td>&lt; 30 pg/mL</td>
</tr>
<tr>
<td>Plasma norepinephrine</td>
<td>383 pg/mL</td>
<td>70 – 750 pg/mL (supine)</td>
</tr>
<tr>
<td>Plasma epinephrine</td>
<td>&lt; 25 pg/mL</td>
<td>&lt; 111 pg/mL (supine)</td>
</tr>
<tr>
<td>Plasma normetanephrine</td>
<td>0.52 nmol/L</td>
<td>&lt; 0.90 nmol/L</td>
</tr>
<tr>
<td>Plasma metanephrine</td>
<td>&lt; 0.20 nmol/L</td>
<td>&lt; 0.50 nmol/L</td>
</tr>
</tbody>
</table>
Pathology

• Right adrenal gland – 3 cm pheochromocytoma
  • “Immunohistochemical stain performed show that the neoplastic cells are diffusely positive for synaptophysin and chromogranin, and the sustentacular cells are highlighted by S100”
  • No adverse histologic features identified such as capsular or vascular invasion, extension into peri-adrenal adipose tissue, large nests or diffuse growth, necrosis, high cellularity, cell spindling, cellular monotony, increased or atypical mitosis, profound nuclear pleomorphism, and nuclear hyperchromasia
  • PASS score of 0
  • Overall, the histological features suggest a benign behavior
Malignant Pheochromocytoma

- Defined as presence of metastases in nonchromaffin tissues
  - Local invasion to surrounding tissues and organs or distant metastases
- Prevalence varies between 10-17%
- Histologically and biochemically similar to benign pheochromocytomas
- May occur as long as 53 years after resection

Young, W. 2019, Lenders et al. 2014
<table>
<thead>
<tr>
<th>Microscopic feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsular invasion</td>
<td>1</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>1</td>
</tr>
<tr>
<td>Extension into the peri-adrenal adipose tissue</td>
<td>2</td>
</tr>
<tr>
<td>Presence of large nests or diffuse growth (in &gt;10% of tumour volume)</td>
<td>2</td>
</tr>
<tr>
<td>Central tumour necrosis (in the middle of large nests) or confluent necrosis</td>
<td>2</td>
</tr>
<tr>
<td>High cellularity</td>
<td>2</td>
</tr>
<tr>
<td>Tumour cell spindling even when focal</td>
<td>2</td>
</tr>
<tr>
<td>Cellular monotony</td>
<td>2</td>
</tr>
<tr>
<td>Increased mitotic figures (&gt;3/10 HPF)</td>
<td>2</td>
</tr>
<tr>
<td>Atypical mitotic figures</td>
<td>2</td>
</tr>
<tr>
<td>Profound nuclear polymorphism</td>
<td>1</td>
</tr>
<tr>
<td>Nuclear hyperchromasia</td>
<td>1</td>
</tr>
</tbody>
</table>

*HPF* high-power field
Fig. 1 Tumour size distribution between three groups

Fig. 2 Tumour weight distribution between three groups

Fig. 3 Immunohistochemical expression of Ki-67 between three groups
Malignant Pheochromocytoma

• The size and weight of the pheochromocytoma are directly related to PASS score and malignancy

• High risk of malignancy or recurrence
  • Presence of tumor necrosis
  • High mitotic rate greater than 3 to 10 HPF
  • Ki-67 index >4%
  • pS100 absence
Follow up

- Endocrinology follow up tomorrow!
- Medical genetics referral
- Annual biochemical testing to assess for recurrent or metastatic disease
References