40 y/o F with headaches and panic attacks

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Disclosures:

I do not have any relevant financial relationships with any commercial interests.

CC/HPI

40 y/o F presents to the ED with complaints of episodic headaches, palpitations, diaphoresis and chest pain

Episodes last 20 mins

Episodes occurred for years and are now becoming more frequent (multiple times during the day)

States that her BP varies widely during the day (anywhere 98-200 / 67 -110)

HPI continued

Symptoms started 4 months prior, after the preterm birth of her baby

- PPROM at 30 weeks followed by an emergent C-section
- Baby passed away Day 2 (unclear cause)

4 months ago…

Day # 11 s/p C-section:

- presented to ED with HTN urgency
- SBP 210 -260/ DBP 111-113

Dx with post-partum preeclampsia

Prescribed Procardia 30 mg daily -> increased to 60 mg daily prior to discharge

Prior to discharge had another episode of HTN urgency treated with IV hydralazine

24-hour urine metanephrines sent…

Labs

	Ref. Range	8/31/17	Result x ULN
24-hr Urine studies			
Metanephrines	30-180 normotensive < 400 hypertensive	5546	13.9
Normetanephrines	119-451 normotensive < 900 hypertensive	29326	32.6
Total metanephrines	156-561 normotensive < 1300 hypertensive	34872	26.8

Diagnostic testing for Pheochromocytoma

24 hr urine fractionated metanephrines and plasma free metanephrines have > 90% sensitivity

Endocrine society suggests use of either

Plasma tests have a higher specificity (79-98% vs 69- 95%)

Table 2. Diagnostic Performance of Plasma Free *Versus* Urinary Fractionated Metanephrines

First Author, Year	Sensitivity		Specificity	
	Plasma	Urine	Plasma	Urine
Lenders, 2002	98.6% (211/214)	97.1% (102/105)	89.3% (575/644)	68.6% (310/452)
Unger, 2006	95.8% (23/24)	93.3% (14/15)	79.4% (54/68)	75.0% (39/52)
Hickman, 2009	100.0% (14/14)	85.7% (12/14)	97.6% (40/41)	95.1% (39/41)
Grouzmann, 2010	95.7% (44/46)	95.0% (38/40)	89.5% (102/114)	86.4% (121/140)
Unger, 2012	89.5% (17/19)	92.9% (13/14)	90.0% (54/60)	77.6% (38/49)

What can cause false positive tests?

Medications can interfere with screening causing a high false positive rate

- Acetaminophen, several classes of antidepressants, stimulants (eg ADHD meds)
- Dopamine agonists, Beta blockers, sympathomimetic, opioids, glucocorticoids

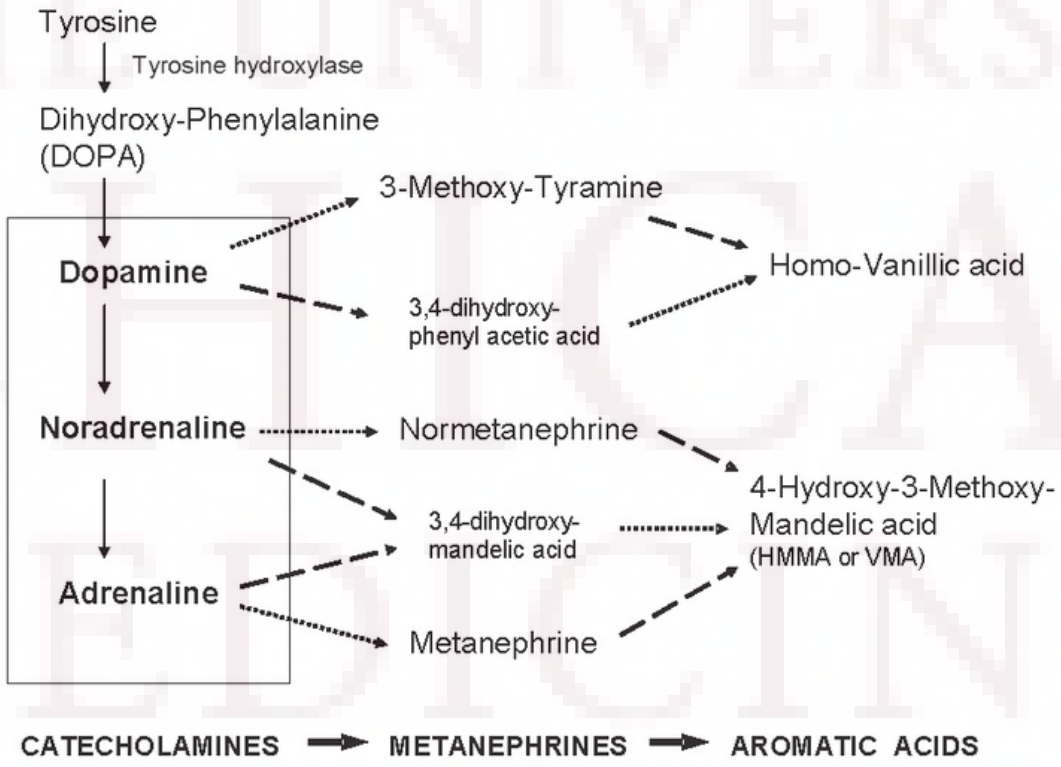
Sympathetic adrenergic overdrive (severe illness, non- supine posture)

Severe renal insufficiency

Table 3. Recommendations for Biochemical Testing Conditions

Patient preparation	Avoid sympathomimetic agents (including ephedrine, amphetamine, nicotine)
	Avoid interfering medication (including labetalol, sotalol, acetaminophen, methyldopa, antidepressants)
	Overnight fast, no caffeinated or decaffeinated beverages
Conditions for blood sampling of metanephrines	Supine condition, after 30 min of rest
	Collection in heparinized tubes on ice
	Storage of plasma in freezer at −200°C if measured within 3 mo
Conditions for urine sampling of metanephrines	Collection in container without additives or eventually only sodium bisulfite
	Storage of urine container in a cold place
	Acidify urine in the laboratory to pH 4 before storing

Catecholamine Biosynthesis & Metabolism



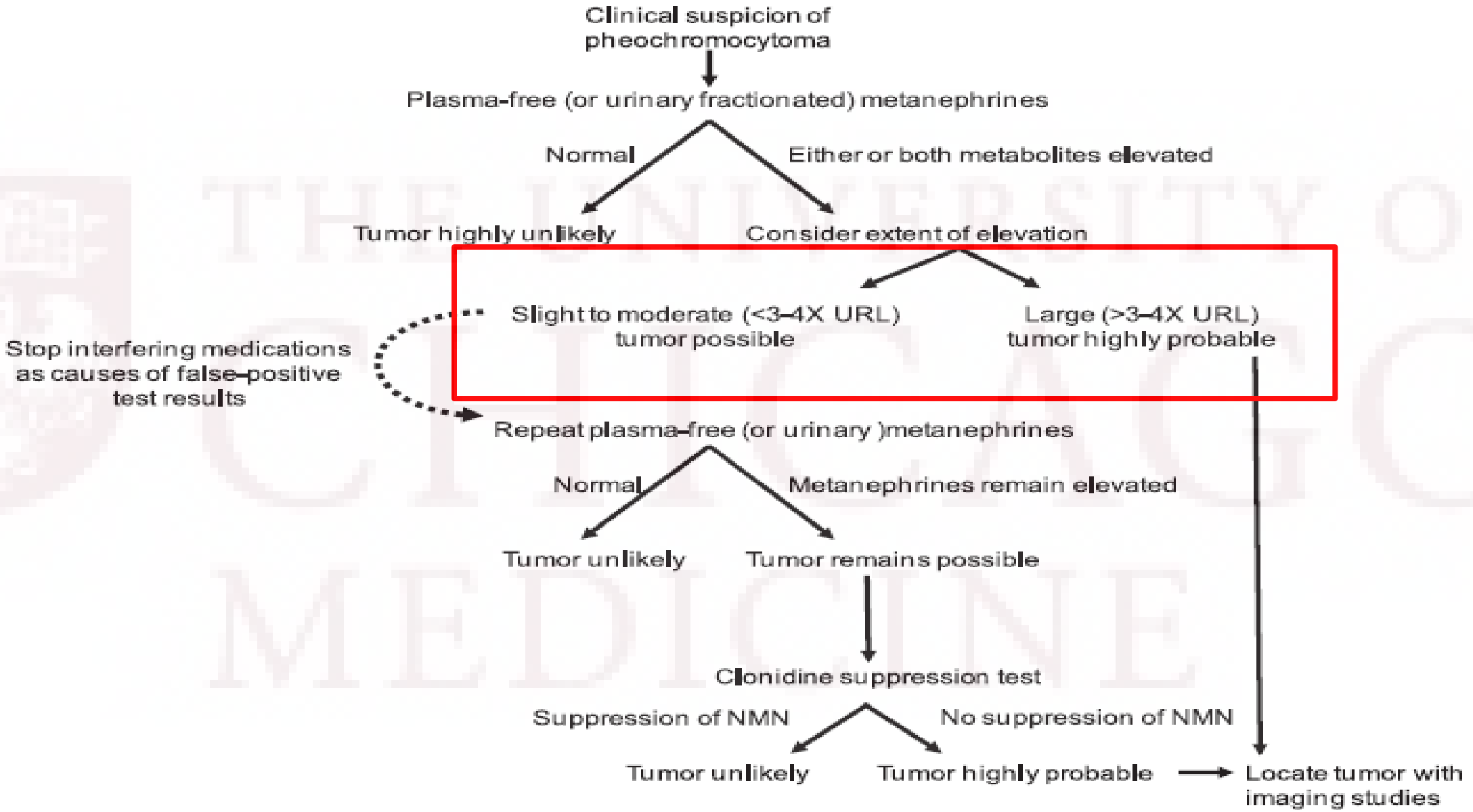


Figure 1. Algorithm for biochemical testing.

Per documentation

'…given the result is not a concerning level for her especially given inpatient admission after emergent surgery and hx of hydralazine administration during her admission. No need to see her in clinic. She should be seen in 3 weeks by PCP and have a random serum methanephrines and normetanephrines drawn. If elevated 2-3 fold higher than the upper limit of normal, she should be seen in hypertension clinic…'

Labs

Plasma studies			
	Ref. Range	9/26/17	Result x ULN
Norepinephrine (pg/mL)	70-750 (supine) 200-1700 (standing)	997	
Epinephrine (pg/mL)	< 111 (supine) < 141 (standing)	30	
Dopamine (pg/mL)	< 30	< 25	
Normetanephrine (mmol/L)	< 0.9	53	X 58
Metanephrine (nmol/L)	< 0.5	5.3	X 10.6

PCC/PGG syndromes

Significance:

Catecholamine excess

- Cardiovascular symptoms/ disease
- Psychiatric symps/disease
- - Malignancy (10- 13%)
- Associated syndromes (Genetic syndromes eg NF1 VHL MEN1)
- Prognosis/ Surveillance implications for the patients and their families

Fast forward 4 months later…

Paged overnight

ED physician wanted to discuss the patient. Seen by outpatient Endocrinologist at OSH. Given her symptoms suggested to come to ED. Here vitals are stable, she had mild chest pain that resolved a few hours ago, stable, eating a sandwich. No EKG changes. Trops neg x 2.

What should be the next step?

PMH/PSH :
Asthma
HTN
C-section

Allergies: iodinated contrast - Hives

Medications:
Procardia XL 60 mg daily
Albuterol inhaler prn

Social hx: lives with fiancé, non-smoker, no alcohol, no OTC medications or recreational drugs. Plans to get married in 8 months.

Family hx

Father died (stabbed) when she was 8 yrs old; she is not in touch with father's family.

Mother has diabetes.

MGM: anxiety attacks, T2DM

M uncle: elevated BP

She has one brother who she believes is healthy

ROS

Constitutional: No fever. Appetite normal, no fatigue.

HENT: No changes in hearing. No sore throat.

Eyes: No changes in vision

Respiratory: No cough, **+ mild palpitations, + intermittent shortness of breath**

Cardiovascular: **+ chest pain,** no orthopnea.

Gastrointestinal: **+nausea, +vomiting,** no diarrhea, no constipation. No blood in the stool.

Genitourinary: No dysuria or hematuria.

Skin: no new rashes.

Neurological: No weakness, **+ intermittent headaches**.

Musculoskeletal: No swelling.

Endo: No chills or hot flashes.

Heme: No easy bruising.

Labs

11/18/2017

Glucose: 483 (H)

Sodium: 132 (L)

Potassium: 3.6

Chloride: 95

Carbon Dioxide: 21 (L)

Anion Gap: 16 (H)

BUN: 9

Creatinine: 0.8

GFR Estimate (Calc): 79

Calcium: 10.0

Beta-Hydroxybutyrate 0.10

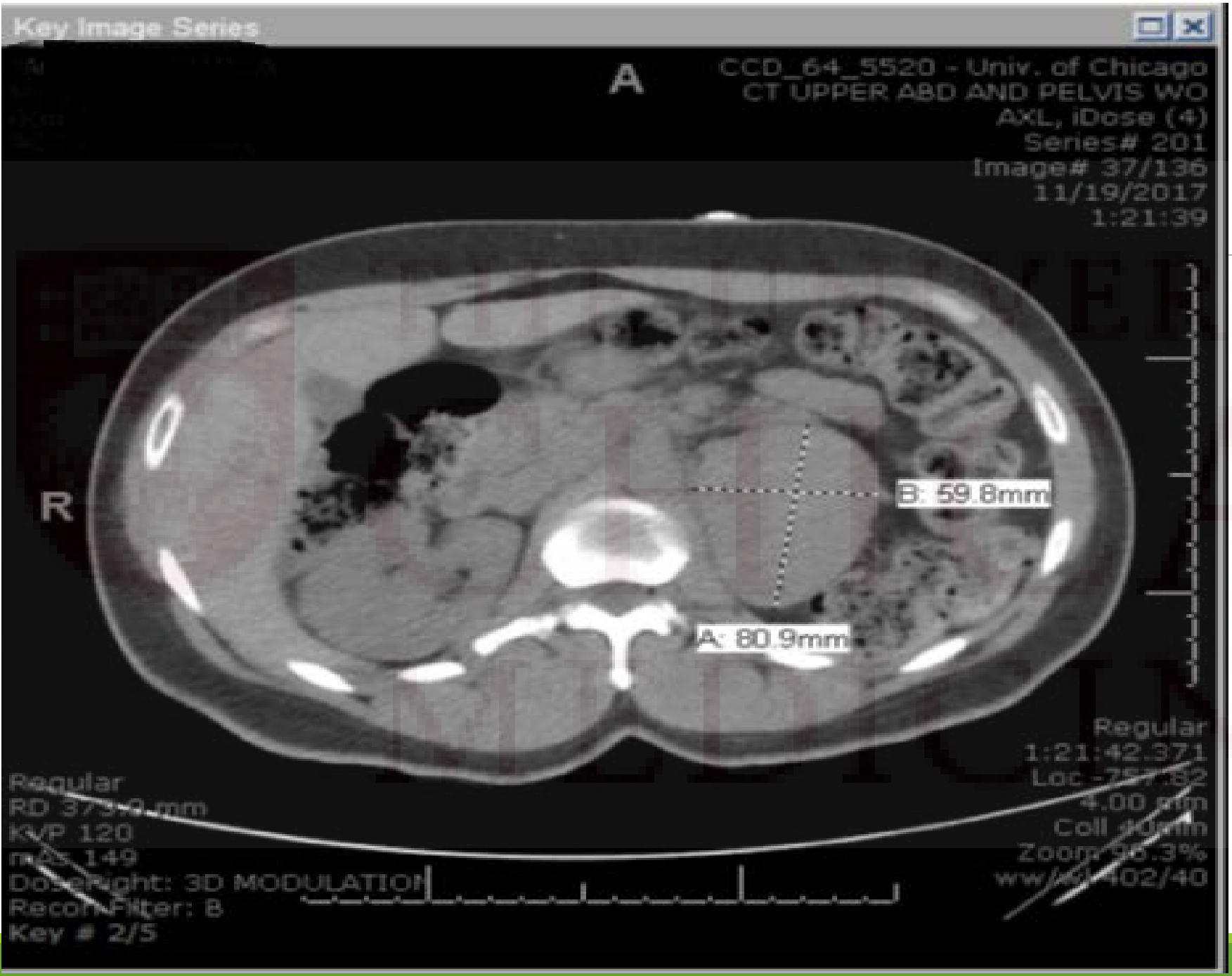
HbA1c: 10.9

Suggested

Patient has classic history and biochemically proven pheochromocytoma

What would be the next step in management?

Imaging with CT scan Abd – to localize the lesion



CT Abd/pelvis

7.9 x 6.1 cm L suprarenal mass concerning for pheo-chromocytoma

Historical Overview: Pheochromocytoma

Mid 1800s – 1st description of the 2 distinct layers of the adrenal gland (cortex & medulla), recognized in patients who died with adrenal destruction secondary to tuberculosis.

1912: Ludwig Pick described pheochromocytoma

Greek, meaning “dusky-colored tumor”

He noted the dark-brown color of the cells with contact with chrome salts

1926-1927: 1st surgical removal of pheochromocytoma in Europe was performed in 1926 and by Mayo in USA in 1927.

Pheochromocytoma/Paraganglioma (PGG)

80- 85% arise from adrenal medullary chromaffin tissues

15-20% extra-adrenal sympathetic derived chromaffin tissues

- Abdomen > pelvis >> rarely mediastinum
- Head & neck PGG = mostly dopamine secreting

Pheochromocytoma/Paragangliomas

Rare but devastating/fatal consequences if not recognized
- Autopsy studies: substantial # undiagnosed

25% of PCC/PGG are malignant

25% are extra-adrenal

40% hereditary
- *pediatric patients = 80% hereditary*

No cure for widely metastatic disease (only 50% 5 year survival)

All patients will need life long screening

Challenges

Symptoms of catecholamine hypersecretion unrecognized as the mimic other conditions

Extra-adrenal gland tumors require more widespread imaging

Mortality:

- Few decades ago: 30 – 45%.
- Now: 0-2.9%

Perioperative blockade

The purpose to block to peripheral effects of catecholamines to minimize excessive intra operative adrenergic receptor agonism that may result in end organ damage, while simultaneously reducing the risk of post op hypotension.

Experienced surgery/ anesthesia team

Usually admitted the day prior, IV fluids , oral salt given to expand the blood volume to prevent pre op orthostatic hypotension and post op hypotension

Post op: Screened with plasma metanephrines 4-8 weeks post surgery to ensure complete resection and then annually

Pre op management

Endocrine Society suggests

-Phenoxybenzamine as 1st line treatment (non selective non competitive alpha blocker)

- Doxazosin or another competitive selective alpha- blocker +/- calcium channel blocker as 2nd line treatment

Metastatic disease

Presence of distant mets in non chromaffin tissue

Risk factors:

- SDHB mutation
- Tumor size (> 4-5 cm)
- secretion of methoxytyramine
- Life-long screening

123 I – MIBG is useful to determine the avidity of the metastatic disease in prep for possible future 131I – MIBG treatment

F- FDG- PET /CT recommended for Succinate Dehydrogenase Subunit (SDHB) mutation (pt population 74- 100% sensitive to PET scans)

Management of metastatic disease

Treatments are not curative

- Debulking surgery
- Chemotherapy with cyclophosphamide, vincristine and dacarbazine (CVD)
- External beam radiation
- 131- MIBG treatment
- Tyrosine kinase inhibitors tested in clinical trials

A Phase II Study Evaluating the Efficacy and Safety of Ultratrace Iobenguane I 131 in Patients With Malignant Relapsed/Refractory Pheochromocytoma/Paraganglioma

Designed to evaluate the effectiveness and collect additional safety information on AZEDRA® (iobenguane I 131) for the treatment of metastatic or relapsed/refractory or unresectable PCP or PGG

This Phase II study will help determine

- Primarily if using the drug reduces the amount of blood pressure medication being taken as a result of the cancer

- Secondarily to determine effectiveness of the study drug, additional safety measures, and to assess if the drug helps the quality of life and use of pain medication.

All subjects will receive an imaging dose with scans followed by two therapeutic doses given approximately 3 months apart.

Should this patient have genetic testing?

Endocrine Society suggests all pts should be engaged in shared decision making regarding genetic testing

Genetics

13 known susceptible genes, most inherited in AD pattern

SDHD and SDHAF2 have paternal inheritance , SDHB highest penetrance, 80% malignancy risk

Gene	Syndrome	Protein (Function)	Tumor Location	Malignancy Rate
NF1	Neurofibromatosis Type 1	Neurofibromin (GTPase which inactivates RAS)	Adrenal (bilateral)	12%
RET	Multiple Endocrine Neoplasia Type 2	RET (transmembrane tyrosine kinase)	Adrenal (bilateral)	<5%
VHL	von Hippel Lindau	pVHL (ubiquitin ligase activity)	Adrenal (bilateral)	5%
SDHx genes *SDHA* *SDHB* *SDHC* *SDHD* *SDHAF2* (*SHD5*)	Familial paraganglioma syndrome	Succinate dehydrogenase complex (complex II of the mitochondrial respiratory chain and converts succinate to fumarate) SDH subunit A (catalytic subunit) SDH subunit B (catalytic subunit) SDH subunit C (anchoring subunit) SDH subunit D (anchoring subunit) SDH cofactor AF2 (cofactor)	Any location Any location, primarily extra adrenal Head and neck, can be thoracic Any location, primarily head and neck Head and neck (multifocal)	Low 23% Low <5% Low
TMEM127		Transmembrane protein 127 (transmembrane protein)	Any location, primarily adrenal	Low
MAX		MYC-associated protein X (transcription factor)	Adrenal (bilateral)	Intermediate
EPAS1	Polycythemia paraganglioma syndrome	Hypoxia inducible factor 2a (transcription factor)	Any location	Not known
FH	Hereditary leiomyomatosis and renal cell carcinoma	Fumarate hydratase (converts fumarate to malate)	Any location	Possibly high
MDH2		Malate dehydrogenase (converts malate to oxaloacetate)	Any location	Not known

Follow-up

Started on doxazosin starting at 1 mg in PM and 2 mg in AM and titrated up PRN

Endocrine surgery:

- Seen in clinic
- Plan for laparoscopic left adrenalectomy
- Possibility of having to convert to an open operation is ~15-20%

Take away points

Most common false positives are due to interfering medicine or drugs

Perioperative management is important for successful surgical outcomes

Up to 40% of pts have germline mutation; all patients with PCP/PGG should be referred to a genetic counsellor irrespective of their family history

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