



Pheochromocytoma Discovered Postpartum

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History

A 28-year-old female G1P1001 presented to the family medicine clinic to establish care and for management of hypertension 6 months after a C-section delivery at 36 weeks. Her pregnancy was complicated by chronic hypertension which evolved into superimposed pre-eclampsia with severe features. She noted that prior to pregnancy her hypertension was well controlled on metoprolol, but during pregnancy she was placed on labetalol, and then replaced with nifedipine, and her blood pressure was still frequently above 140/90 with symptoms of "shakiness" when her blood pressure would rise. Physical examination at this visit, aside from a blood pressure of 145/96, was unremarkable. Family history was remarkable for cardiovascular disease, specifically hypertension and heart failure. Social history was unremarkable for tobacco use, alcohol use, and illicit drug use. Labs at this visit, including CBC, CMP and lipids, were unremarkable. She was placed back on metoprolol, and her blood pressure did well for about 1 month.

She then presented to clinic with episodes or "spikes" of hypertension described as a persisting constellation of symptoms lasting five to ten minutes, which included a drop in her heart rate followed by increased blood pressure accompanied by shortness of breath, intense palpitations, dizziness, and chest pain. These were precipitated by no known cause and resolved without any specific treatment. She did not feel anxious prior to these episodes, and the episodes would occur three to five times per day. Following this visit, she was switched to amlodipine, however she developed a rash and was placed back on metoprolol with clonidine to use as needed for treating her "spikes" of high blood pressure.

At this time, further testing was initiated, and a referral to cardiology was generated.

Diagnostic Testing

EKG revealed normal sinus rhythm with sinus arrhythmia.

A Holter monitor showed sinus rhythm with very rare premature supraventricular beats and an average heart rate of 82 bpm. Reported symptoms (weakness, fatigue, lightheadedness, shortness of breath, tingling) correlated with normal sinus rhythm.

Zio Patch monitoring was negative for significant arrhythmia, with average HR 79, and one 4 beat SVT run at 150s bpm.

Transthoracic Echo performed was normal and unremarkable.

Renal ultrasound with doppler was performed and showed no evidence of renal artery stenosis and unremarkable kidneys. There was, however, an incidental finding of an apparent 4 cm complex abnormality in the mid abdomen slightly to the left of the aorta, for which CT correlation was suggested (Figure 1).

CT Abdomen & Pelvis with and without IV contrast showed an indeterminate 4.3 cm heterogeneously enhancing partially cystic left adrenal mass (Figure 2).

Laboratory tests performed included urine and blood catecholamines and metanephrines (Table 1).

Subsequent MRI Renal with and without IV contrast showed a left suprarenal 4.5 cm complex solid and cystic lesion compatible with an adrenal versus extra-adrenal cystic pheochromocytoma (Figure 3,4).

Treatment

Imaging studies in combination with laboratory testing was suggestive of a left pheochromocytoma. Consultation with endocrinology and urology was sought. The patient's medication regimen was titrated to doxazosin 5 mg twice a day and metoprolol 25 mg twice a day for control of hypertension prior to surgery. A robotic left adrenalectomy was performed.

The final pathology report revealed a 37.0 gm mass formed of well encapsulated round tumor measuring 6.0 x 4.0 x 3.0 cm showing preserved Zellballen pattern with few

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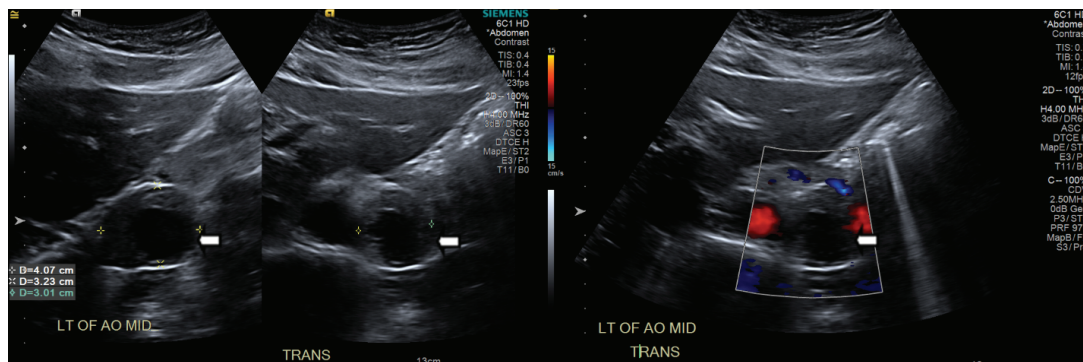


Figure 1: Initial ultrasound images demonstrate an incidental finding of a left adrenal mass with measurements demonstrated in longitudinal and transverse planes on the left image (arrows). The image on the right demonstrates no internal vascularity on color doppler imaging (arrow).

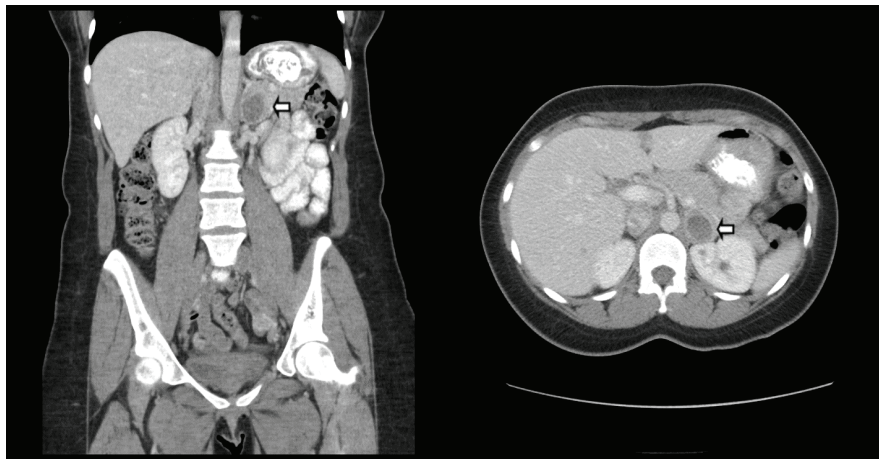


Figure 2: Coronal CT image with contrast (left image) of the abdomen and pelvis demonstrates a left adrenal mass (arrow) with a peripheral solid component and internal cystic versus necrotic component. Axial CT image with contrast of the upper abdomen also demonstrates the left adrenal mass (arrow).

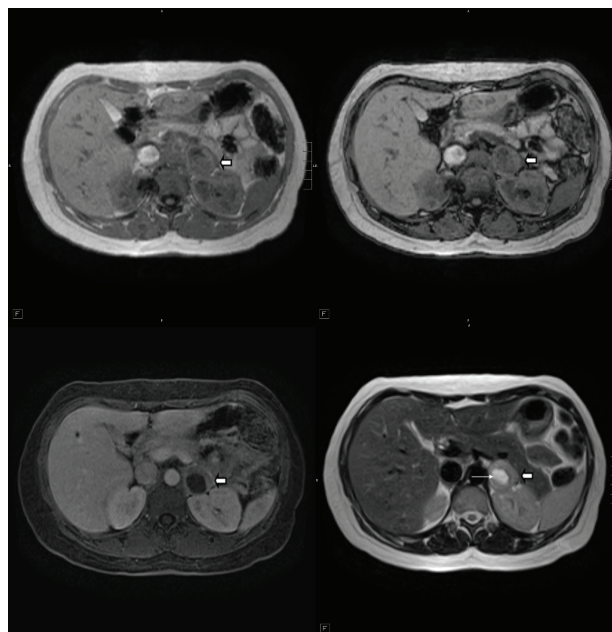


Figure 3: MRI images of the abdomen with and without contrast demonstrate a left adrenal mass (short thick arrows). The lesion is mixed T1 intensity on the pre contrast T1 image (top left). There is no signal dropout on out of phase imaging (top right image). The post contrast fat saturated T1 image (bottom left) demonstrates enhancement of the solid peripheral component and lack of enhancement of the central cystic/necrotic component. The T2 weighted image (bottom right) demonstrates T2 high signal "light bulb" bright centrally in the cystic/necrotic component (thin arrow).

Lab	Reference Range	Patient Value
Metanephrine Urine, 24 Hr	45-290 ug/24 hr	1300 ug/24 Hr
Normetanephrine, Urine 24 Hr	82-500 ug/24 hr	1177 ug/24 Hr
Epinephrine Urine, 24 Hr	0-20 ug/24 hr	104 ug/24 hr
Norepinephrine Urine, 24 Hr	1-135 ug/24 hr	262 ug/24 hr
Dopamine Urine, 24 Hr	0-510 ug/24 hr	408 ug/24 hr
Plasma Epinephrine	0-62 pg/ml	173 pg/ml
Plasma Norepinephrine	0-874 pg/ml	639 pg/ml
Plasma Dopamine	0-48 pg/ml	<30 pg/ml

Table 1: Initial Lab Values

Lab	Reference Range	Post Operative Value
Metanephrine Urine, 24 Hr	45-290 ug/24 hr	91 ug/24 Hr
Normetanephrine, Urine 24 Hr	82-500 ug/24 hr	221 ug/24 Hr
Epinephrine Urine, 24 Hr	0-20 ug/24 hr	4ug/24 hr
Norepinephrine Urine, 24 Hr	1-135 ug/24 hr	18 ug/24 hr
Dopamine Urine, 24 Hr	0-510 ug/24 hr	354 ug/24 hr

Table 2: Post-Operative Lab Values

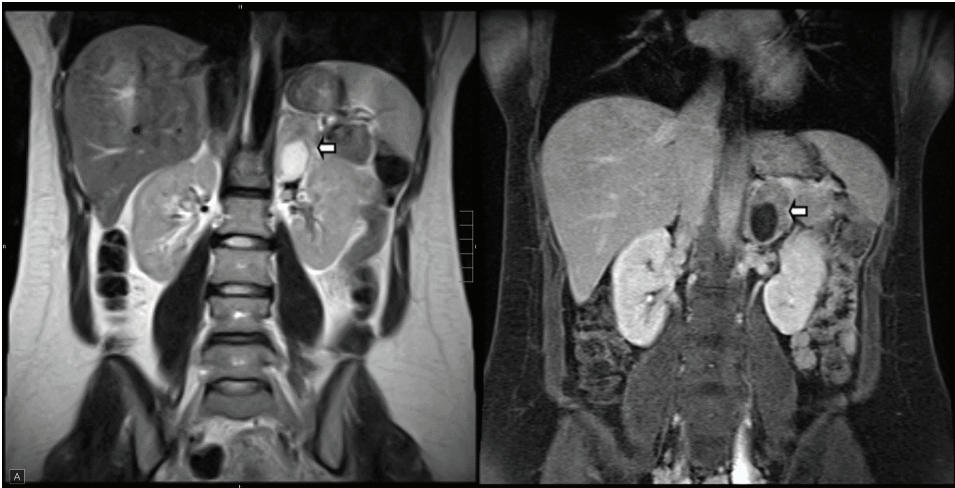


Figure 4: Coronal MRI images of the abdomen demonstrate the left adrenal mass (arrows) which is T2 bright centrally (left image) and demonstrates peripheral enhancement of the solid component with lack of enhancement centrally of the necrotic/cystic component (right image).

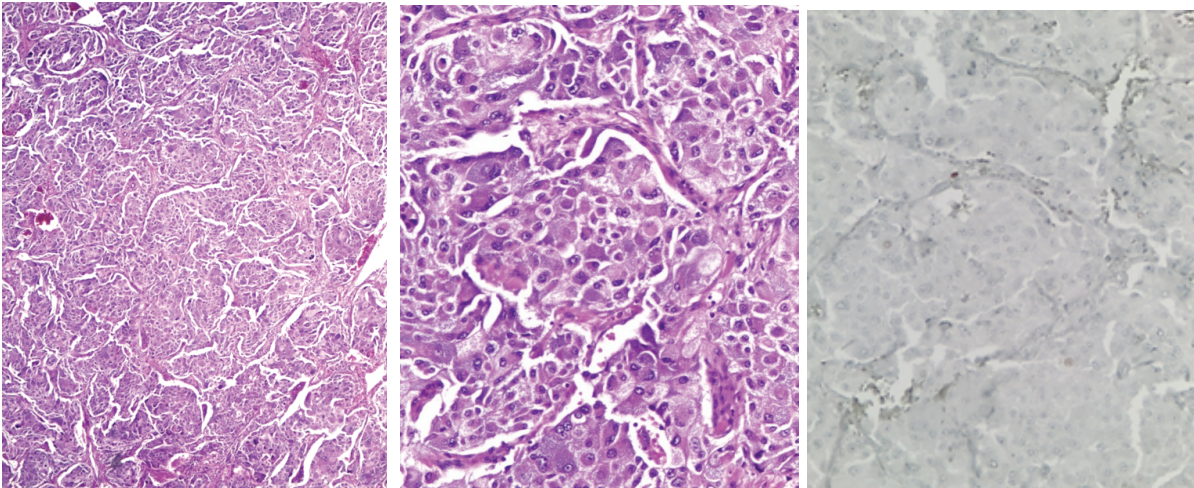


Figure 5: Pathology Slides. Zellballen nested pattern of tumor cells (Left: H&E stain x2.5) showing abundant basophilic cytoplasm with mild nuclear pleomorphism (Middle: H&E stain x10) and very low proliferation index (Right: KI-67 immunostain x10).

foci of large irregular nests, but no diffuse growth seen (Figure 5). Histology was negative for tumor necrosis, high cellularity, cellular monotony, spindling, profound nuclear pleomorphism, nuclear hyperchromasia or vascular invasion. Mitoses were inconspicuous and Ki67 proliferation marker labels less than 1% of the tumor cell nuclei. No tumor extension into adipose tissue was seen. A focus of capsular invasion was noted. These features were consistent with a well differentiated type per the official Grading of Adrenal Pheochromocytoma and Paraganglioma (GAPP) risk stratification tool.

Outcome of the Case

The patient tolerated the procedure well, with no complications reported. She was discharged on no blood pressure medicine. Several months post-operatively, she continues to remain normotensive, with resolution of episodes of “blood pressure spikes”, chest pain, chest discomfort, and palpitations.

Follow up laboratory testing several weeks post-surgery reveal resolution of her elevated catecholamine levels (Table 2).

The patient underwent genetic testing for mutations in the Von Hippel-Lindau (VHL) gene, results revealing no detectable sequence variants. Repeat labwork, including CBC, BMP, and catecholamines eleven months status post left adrenalectomy were all within normal limits. Her blood pressure remains on average in the 130s/80s on no medications since surgery.

Discussion

Pheochromocytomas are an important, albeit rare, cause of secondary hypertension. Pheochromocytomas are catecholamine-secreting, neuroendocrine tumors typically arising from the adrenal medulla, with about 15-20% of such tumors occurring outside of the adrenal gland [1]. The prevalence of pheochromocytomas in hypertensive patients ranges from 0.1% to 0.2% [2]. These tumors can cause serious cardiovascular complications including myocardial infarction, cardiac failure, aortic dissection and sudden death [3]. Common symptoms include hypertension, headaches, palpitations and sweating. Other symptoms of pheochromocytoma include nausea, fatigue, weight loss, and flushing [4]. The differential diagnosis of pheochromocytomas includes: anxiety disorders, Von Hippel-Lindau disease, essential hypertension, hyperthyroidism, insulinoma, paroxysmal supraventricular tachycardia, renovascular hypertension and carcinoid tumors [5]. Pheochromocytoma can be associated with several inherited syndromes including Von Hippel-Lindau syndrome, multiple endocrine neoplasia type 2, and neurofibromatosis type 1 [2]. These syndromes are all transmitted in an autosomal dominant fashion, and up to 25% of cases of pheochromocytoma are associated with these syndromes [6]. Genetic testing should be offered to patients who are diagnosed with pheochromocytoma. However, even with a normal genetic screen, pathogenic variants in VHL may be missed due to limitations inherent to the analysis method, and therefore the presence of VHL Syndrome due to a different genetic cause cannot be ruled out. Furthermore, the sequence analysis method is limited by the inability to detect large deletions in the sequence that occur on only one chromosome, which are a common cause of VHL Syndrome. Therefore, all patients should continue with lifelong measurements of catecholamines due to the lack of predictability.

Diagnosing pheochromocytoma can be difficult due to the episodic pattern of secreting catecholamines. The diagnosis is confirmed by an elevated serum fractionated metanephrines or elevated 24-hour urinary fractionated metanephrines [5]. Rarely, some pheochromocytomas secrete dopamine only, and thus serum and 24-hour urine can be helpful in cases where the metanephrines are not elevated [7]. Because it can be difficult to detect, pheochromocytoma is sometimes first picked up incidentally by imaging done for other conditions.

Imaging of pheochromocytoma typically consists of anatomical imaging modalities such as CT or MRI and functional imaging including I-MIBG and multiple PET ligands. Typically,

pheochromocytomas when smaller are more solid appearing and when larger contain cystic or necrotic components centrally. Size can vary from 1.2 to 15 cm as reported in a previous study [8,9]. Ultrasound is typically less helpful and can demonstrate an adrenal lesion with potential delineation of solid components, cystic components, or hemorrhagic components. Diagnosis via CT and MRI imaging is also difficult due to overlapping imaging characteristics of pheochromocytoma and other adrenal masses. Approximately two thirds of pheochromocytomas are solid and the rest are complex or cystic [8,10]. Nearly all pheochromocytomas have Hounsfield units (HU) greater than 10 on non-contrast CT, helping to differentiate these from Lipid rich adenoma with rare exceptions [8,11,12]. Hemorrhage and calcification can also sometimes be seen in pheochromocytomas. On contrast enhanced CT the majority of these demonstrate avid enhancement in the solid components [8]. On MRI imaging, the appearance of pheochromocytoma can vary depending on solid versus cystic appearance along with hemorrhagic or calcified components. T2 appearance has been classically described as “light bulb” bright; however, this appearance varies in 11-65% of pheochromocytomas [8,9,13]. Both T1 and T2 signals are variable dependent on cystic, necrotic, or hemorrhagic components [8].

Functional imaging has higher sensitivity and specificity for pheochromocytoma and can be helpful due to the variable appearance of these on anatomical imaging as previously discussed. Imaging using MIBG (Metaiodobenzylguanidine) using 131-I MIBG or 123-I-MIBG is a common and available nuclear medicine imaging technique to help assist in the diagnosis of pheochromocytoma. The sensitivity of 123-I-MIBG ranges from 77-90% with specificity of 95-100% [8,14-17]. Additionally, SPECT/CT technology has improved sensitivity and specificity. PET/CT imaging is also being increasingly used with PET ligands 18F-DOPA and 18F-FDG [18-20]. Additionally, 18F-DOPA imaging has yielded improved sensitivity over MIBG [8,15,21-23].

Definitive treatment for pheochromocytoma is by adrenalectomy. Management of the catecholamine effects for at least 10-14 days prior to surgery is important to prevent intra-operative risks, which include hypertension, low blood volume, and catecholamine-induced cardiomyopathy [3]. Typically, alpha-blockers followed by beta-adrenergic blockade are the first line of treatment prior to surgery, and/or calcium channel blockers may be used as well.

Following adrenalectomy, pheochromocytoma can reoccur either locally or distally, in up to 16.5% of patients, and more commonly in patients whose tumor size is greater than 5 cm [24,25]. Routine imaging with serum and urine testing is recommended for these patients.

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