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Case Report

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Management of 3 Cases of Pheochromocytoma During the COVID-19 Pandemic in New York City: Lessons Learned

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Abbreviations: FH, fumarate hydratase; PASS, Pheochromocytoma of the Adrenal Gland Scaled Score.

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Abstract

The COVID-19 crisis placed a pause on surgical management of nonemergency cases of pheochromocytoma, and it was essential for endocrinologists to provide both resourceful and safe care. At the Mount Sinai Hospital in New York City during the peak of the pandemic, we encountered 3 patients with pheochromocytoma and mild symptoms that were medically managed for a prolonged period of time (7-18 weeks) prior to adrenalectomy. Patients were monitored biweekly via telemedicine, and antihypertensive medications were adjusted according to signs, symptoms, and adrenergic profiles. These cases demonstrate that prolonged medical management prior to surgery is feasible and effective in pheochromocytoma patients with mild symptoms and well-controlled blood pressures.

Key Words: pheochromocytoma, COVID-19, adrenal mass

The COVID-19 crisis has reshaped our approach to treating urgent endocrine diseases such as pheochromocytomas. Due to their capacity to release large amounts of catecholamines into the circulation, pheochromocytomas should be treated rapidly once identified. There are some differences of opinion regarding the optimal drug and duration of preoperative medical therapy [1-3]. However, the Endocrine Society guidelines advocate a brief period of medical preparation (7-14 days) prior to definitive treatment with surgical adrenalectomy [4].

We herein describe 3 patients that presented in March 2020 to the Adrenal Center at the Mount Sinai Hospital in New York City with newly diagnosed pheochromocytomas. These 3 cases occurred during the height of the COVID-19 pandemic, when resources and personnel were redeployed. By late March, all nonemergency surgeries were canceled in New York State. Furthermore, the "New York State on Pause" took effect, an executive order closing all nonessential businesses, restricting public gatherings, encouraging

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social distancing, and urging sick, immunosuppressed, and elderly individuals to stay home and visit their doctors via telemedicine. As a result, preoperative medical management of pheochromocytoma was prolonged, remote, and tailored to the individual cases (Table 1). All 3 patients had uncomplicated preoperative courses and completed surgery by July 2020 with successful outcomes.

Case 1

A 60-year-old female with hypertension and prediabetes initially presented to urology for evaluation of hematuria. Imaging demonstrated a right renal mass suspicious for renal cell carcinoma and an adrenal mass. On follow-up magnetic resonance imaging of the abdomen with and without contrast, the adrenal mass measured 6.7 × 6 × 5 cm, and was hypervascular without loss of signal.

Table 1. Patient characteristics

	Case 1	Case 2	Case 3
Date of first visit to the Adrenal Center	Last week of March 2020	First week of March 2020	Second week of March 2020
Interval between first visit and surgical adrenalectomy	7 weeks	13 weeks	18 weeks
Type of visit	Telehealth	Office	Office
Current age (years)/sex	60/Female	67/Female	84/Female
Symptoms	Hypertension and weight loss. History of prediabetes	Hypertension, weight loss, and episodes of palpitations, diaphoresis, and anxiety. History of type 2 diabetes	Hypertension, weight loss, intermittent hand tremors, and palpitations
BP medications at presentation	Amlodipine 5 mg daily	Lisinopril 40 mg daily	Ramipril 2.5 mg daily
BP medications preoperatively	Amlodipine 7.5 mg daily	Terazosin 1 mg daily and metoprolol tartrate 12.5 mg twice daily	Amlodipine 2.5 mg daily and ramipril 2.5 mg
Vital signs	BP 144/73 mmHg, HR 97 bpm	BP 105/55 mmHg, HR 100 bpm	BP 110/70 mmHg, HR 68 bpm
Tumor size (on imaging)	6.7 × 6 × 5 cm	6.3 × 4.8 cm	4 × 3.1 × 4.8 cm
Tumor size (on pathology)	6.8 cm	8 cm	5.7 cm
Pathology/PASS score	Pheochromocytoma, PASS 0	Pheochromocytoma, PASS 10 (atypical mitosis, large nest, cellular monotony, focal tumor spindling, nuclear hyperchromasia, nuclear pleomorphism)	Pheochromocytoma, PASS 1
Plasma and/or urine normetanephrines	Urine: 2276 µg/24 hour (122-676)	Plasma: 2418 pg/mL (0-145) Urine: 8610 µg/24 hour (82-500)	Plasma: 678 pg/mL (0-145) Urine: 824 µg/24 hour (82-500)
Plasma and/or urine metanephrines	Urine: 158 µg/24 hour (90-315)	Plasma: 245 pg/mL (0-62) Urine: 2076 µg/24 hour (45-290)	Plasma: 370 pg/mL (0-62) Urine: 1564 µg/24 hour (45-290)
Normetanephrine to metanephrine ratio	14:1 (urine)	10:1 (plasma) 4:1 (urine)	1.8:1 (plasma) 1:1.9 (urine)
Management	Preoperatively, increase in amlodipine from 5 to 7.5 mg daily. Underwent surgical adrenalectomy and partial nephrectomy in May 2020	Preoperatively, initiation of terazosin 1 mg daily and metoprolol tartrate 12.5 mg twice daily. Underwent surgical adrenalectomy in June 2020	Preoperatively, maintenance on ramipril 2.5 mg daily, and initiation of amlodipine 2.5 mg daily. Underwent surgical adrenalectomy in July 2020

Abbreviations: BP, blood pressure; HR, heart rate.

Her initial endocrine visit was via a telehealth video visit. The patient had hypertension for 7 years that was well controlled on amlodipine 5 mg and decreased salt intake. She reported an unintentional weight loss of 4 to 8 pounds in 1 year. She otherwise did not report symptoms of palpitations, tremors, diaphoresis, or headaches.

Laboratory testing showed elevated urine normetanephrine 2276 µg/24 hours (122-676) with normal urine metanephrine 158 µg/24 hours (90-315). Twenty-four–hour urine free cortisol was normal.

Preoperatively, the patient was maintained solely on calcium channel blockade, but the dosage of amlodipine was increased from 5 mg to 7.5 mg daily because of systolic hypertension on the lower dosage. She received biweekly phone calls to monitor her vital signs and symptoms, and medication dosage changes were made accordingly.

The patient underwent an uncomplicated right adrenalectomy and partial nephrectomy 7 weeks from her first endocrinology visit. Pathology confirmed an eosinophilic, low-grade renal cell carcinoma and a 6.8 cm pheochromocytoma. Histologically, the Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) score was 0, for which a score below 4 suggests benign behavior [5]. The patient also underwent genetic testing with a commercial multigene cancer panel that employed full-gene sequencing and deletion/duplication analysis. Gene mutation analysis disclosed a germline mutation in the fumarate hydratase (*FH*) gene at c.698G>A (p.Arg233His). This variant is classified as pathogenic for hereditary leiomyomatosis and renal cell cancer in ClinVar, and there is additional evidence supporting a correlation with paraganglioma–pheochromocytoma in patients with this variant [6, 7]. Of note, she did have a hysterectomy for fibroids at age 31 years. However, her renal tumor demonstrated retention of FH immunostaining, indicating that the FH mutation may not have been pathogenic in this case.

Postoperatively, she was successfully titrated off amlodipine within 2 weeks and remained normotensive off any antihypertensive medications. In addition, her fasting glucose improved from 105 to 87 mg/dL. By 6 weeks after surgery, she reported a good appetite but her weight remained below her typical adult weight.

Case 2

A 67-year-old female initially presented to gastroenterology with left lower quadrant abdominal pain and hip pain for 4 months. Computed tomography of the abdomen with contrast demonstrated a 6.3 × 4.8 cm heterogeneously enhancing left adrenal mass that measured 87 Hounsfield units, with 18% relative washout on delayed imaging.

The patient had type 2 diabetes and hypertension, which were well-controlled on metformin 1000 mg twice daily and lisinopril 40 mg daily, respectively. She also was diagnosed with primary hyperparathyroidism, with parathyroid hormone 159 pg/mL and calcium 11.3 mg/dL at peak. No parathyroid adenoma was identified on ultrasound. She reported an unintentional weight loss of 40 pounds over 2 years, fatigue, and occasional episodes of palpitations, diaphoresis, and anxiety.

Laboratory testing showed elevated plasma and urine normetanephrines 2418 pg/mL (0-145) and 8610 µg/24 hours (82-500), respectively, plasma and urine metanephrines 245 pg/mL (0-62) and 2076 µg/24 hours (45-290), respectively, urine dopamine 1701 µg/24 hours (0-510), urine epinephrine 102 µg/24 hours (0-20), and urine norepinephrine 1631 µg/24 hours (0-135). Renin, aldosterone, and 1 mg overnight dexamethasone suppression testing were normal.

Preoperatively, selective alpha-1-adrenergic receptor blockade with terazosin 1 mg daily was initiated, followed by beta-1-adrenergic receptor blockade with metoprolol tartrate 12.5 mg twice daily. Symptoms improved on this regimen.

The patient was scheduled for adrenalectomy 8 weeks after her initial visit but this was delayed as the patient tested positive for COVID-19 during routine presurgical screening. She was asymptomatic, and thus did not require supportive treatment or medications for COVID-19.

Telephone visits were conducted with the patient by either the endocrinologist or primary care physician at biweekly intervals to review the patient's daily monitoring of home blood pressure, heart rate, and symptoms. She underwent an uncomplicated left adrenalectomy 4 weeks later (12 weeks after she first presented). Pathology confirmed an 8 cm pheochromocytoma with a high PASS score of 10, which suggested a higher potential for malignant behavior. The patient was found to have unremarkable genetic testing utilizing a commercial multigene panel that included *MEN2, VHL, NF1, NF2, SDHx,* as well as 73 other genes.

Postoperatively, plasma normetanephrine and metanephrine levels normalized. She was maintained on lisinopril 10 mg daily and remained normotensive on that regimen. Her fasting glucose also improved from 166 to 93 mg/dL. By 6 weeks after surgery, she had gained back 8 pounds. She is pending further evaluation for her primary hyperparathyroidism.

Case 3

An 84-year-old female with hypertension, hyperlipidemia, hypothyroidism, and anxiety was incidentally found

to have a right adrenal mass in 2010. The mass slowly doubled in size on intermittent repeat imaging over the ensuing 10 years. However, the patient had not been referred to endocrinology until late January 2020, when imaging showed further growth to 4 × 3.1 × 4.8 cm, and a pheochromocytoma work-up was initiated.

The patient had mild, long-standing hypertension that was well controlled on ramipril 2.5 mg daily. She reported an unintentional weight loss of 18 pounds in the past 2 to 3 years, and intermittent hand tremors and palpitations. Family history was notable for a daughter who had a successful resection of a cardiac paraganglioma at age 38 years old. In March 2019, the patient underwent open reduction and internal fixation of a fractured right hip without complication. In August 2019, she underwent an emergency exploratory laparotomy for small bowel obstruction and had 3 feet of necrotic bowel removed, which was complicated by a fistula that closed after 7 months.

Laboratory testing in February 2020 showed elevated plasma and urine normetanephrines 678 pg/mL (0-145) and 824 µg/24 hours (82-500), respectively, and plasma and urine metanephrines 370 pg/mL (0-62) and 1564 µg/24 hours (45-290,) respectively. Twenty-four–hour urine dopamine, epinephrine, and norepinephrine were normal. Renin, aldosterone, and 1 mg overnight dexamethasone suppression testing were normal.

Preoperatively, the patient was maintained on ramipril at the same dosage and started on amlodipine 2.5 mg daily. She received weekly phone calls to monitor her vital signs and symptoms, and medication dosage changes were made accordingly. Given her family history of paraganglioma, she underwent positron emission tomography-dotatate imaging that showed uptake in the known area of the pheochromocytoma and nonspecific uptake along the medial aspect of the liver superior to the lesion.

The patient underwent an uncomplicated adrenalectomy 18 weeks from her first endocrinology visit. Pathology confirmed a 5.7 cm pheochromocytoma with a PASS score of 1, suggesting benign behavior.

Postoperatively, her ramipril was discontinued and her blood pressure was controlled with amlodipine 2.5 mg daily. Plasma normetanephrine and metanephrine levels normalized. By 3 weeks after surgery, she had gained back 3 pounds. Genetic testing was recommended but the patient deferred further evaluation.

Discussion

We herein present 3 cases of incidentally discovered pheochromocytomas that were biochemically confirmed during the COVID-19 crisis in March 2020 in New York City. The traditional treatment for this disorder is surgical adrenalectomy after a 2-week period of alpha-adrenergic receptor blockade to minimize perioperative complications. However, the unusual circumstances created by the pandemic necessitated a more prolonged preoperative period of medical management. Patients were able to measure their blood pressures and heart rates on a daily basis, and to communicate frequently with their providers via telemedicine. The endocrinology on-call service was available to assist with alarming vital signs or symptoms.

The strategies for each of the 3 patients were determined by their age, symptoms, signs, comorbidities, and biochemical profiles (Table 1). In terms of symptoms, Case 1 was asymptomatic, whereas Cases 2 and 3 reported occasional tremors, sweating, and palpitations. All denied headache, a feature of the classic triad of pheochromocytoma symptoms (diaphoresis, palpitations, and headache). All 3 cases had only mild hypertension that was well controlled with medical therapy.

Signs and symptoms associated with pheochromocytomas/paragangliomas may correspond to the catecholamine profiles (noradrenergic vs adrenergic). The only sign that was common to all cases was unexplained weight loss. This correlates with their common biochemical feature, noradrenergic excess, that has been shown to increase thermogenesis by brown adipose tissue via activation of beta-3-adrenergic receptors [8, 9]. The mechanisms underlying impaired glucose homeostasis in patients with pheochromocytomas are more complex. Epinephrine is 10 times more potent than norepinephrine at inhibiting insulin secretion, peripheral glucose utilization, and GLP-1 secretion, while inducing lipolysis and hepatic gluconeogenesis [10]. Interestingly, only Cases 1 and 2 demonstrated impaired glucose homeostasis, and Case 1 had an exclusively noradrenergic secretory profile.

Cases 1 and 2 had predominantly noradrenergic secretory profiles compared with Case 3, where both normetanephrines and metanephrines were elevated. This was consistent with a recent report by our group demonstrating that larger size tumors (Cases 1 and 2) had higher ratios of normetanephrine/metanephrine than smaller tumors (Case 3) [11]. In addition, Case 1 harbored a fumarate hydratase variant, a mutation that falls into the cluster 1 classification (pseudohypoxia-related tumors) that tend to have a more noradrenergic secretory profile regardless of size [6, 7].

Case 2 was the largest tumor with the highest PASS score, predominantly normetanephrine secretory profile, and also elevated serum dopamine levels. Prior studies have shown that dopamine hypersecretion is associated with more aggressive and malignant disease [12, 13]. Case 2 had occasional palpitations and paroxysmal hypertension. She was treated with the most traditional regimen, alpha-receptor

blockade followed by beta-receptor blockade with an excellent clinical response. Her surgery was originally planned for early May but mandatory preoperative testing demonstrated that she was COVID-19 positive in the absence of symptoms. Therefore, she had 2 delays in surgery that were related to the pandemic. The first delay was due to the cancellation of nonemergency surgeries and the second delay resulted from her positive COVID-19 test. In spite of these 2 delays and the more aggressive final pathology, she did well clinically preoperatively, intraoperatively, and postoperatively.

Case 3 was the most challenging to manage for several reasons: she was older (age 84 years old), lived a distance from the medical center, and had limited means of transportation. Her surgery was more delayed than that of the other 2 patients due to her advanced age and the need for further imaging to rule out extra-adrenal paraganglioma prior to adrenalectomy, given the positive family history. She clearly had an undiagnosed pheochromocytoma for at least 10 years prior, yet underwent 2 major surgeries in 2019 without any serious cardiac or neurologic sequelae. Her tumor was biochemically more adrenergic than the others. Thus, she was prone to tachycardia and hypotension due to the vasodilatory effects of epinephrine on the beta-2-adrenergic receptor [9, 14]. Accordingly, a more conservative medical approach was taken with the addition of a small dose of a calcium channel blocker to her angiotensin converting enzyme inhibitor regimen.

Both Cases 1 and 3 did not undergo alpha-adrenergic blockade preoperatively, given that they both had mild hypertension and minimal symptoms. The 2014 Endocrine Society clinical practice guidelines for pheochromocytoma and paraganglioma state that alpha-adrenergic blockade is the first choice for preoperative blood pressure management, but note that some studies have suggested that calcium channel blockade can be used as first-line therapy. Monotherapy with calcium channel blockade is not recommended unless patients have very mild preoperative hypertension as in Cases 1 and 3 [4]. In addition, since these guidelines, a retrospective analysis comparing alpha-adrenergic with calcium channel blockade preoperatively has shown that intraoperative hemodynamic instability was independent of the type of blockade [2]. In all cases, regardless of the preoperative antihypertensive regimen, there were no notable intraoperative challenges, and the patients underwent standard of care intraoperative management with successful outcomes.

The "New York State on Pause" restrictions due to the COVID-19 pandemic necessitated an adjustment to our standard approach to the management of pheochromocytoma. It also created a reliance on telemedicine, with video visits and at least biweekly telephone follow-ups substituting for in-person examinations. All 3 patients were involved in their preoperative care by conducting at-home monitoring of their blood pressures and heart rates, and communicated their results to their providers. In addition, all patients were informed about the signs and symptoms suggestive of a catecholaminergic crisis, and had ready access to their providers.

The specific challenges presented by the COVID-19 pandemic required that patients engage more actively and that their doctors revise their approaches to preoperative outpatient management. Both endocrinologists and their patients with pheochromocytomas had to rapidly adjust to this new normal to reset the clock on the "ticking time bomb" and ensure a safe outcome. These cases demonstrate that prolonged medical management prior to surgery in extenuating circumstances is feasible and effective in pheochromocytoma patients with mild symptoms and well-controlled blood pressures.

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Additional Information

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