Management of three cases of pheochromocytoma during the COVID-19 pandemic in New York City: lessons learned

Emily A Japp MD, Amanda Leiter MD, Effie A Tsomos MD, Sarah A Reda MD, and Alice C Levine MD

Division of Endocrinology, Diabetes, and Bone Disease, Department of Medicine at the Icahn School of Medicine at Mount Sinai, New York, N.Y. 10029

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Address all correspondence and requests for reprints to: Emily A Japp MD, Division of Endocrinology, Diabetes, and Bone Disease, Department of Medicine at the Icahn School of Medicine at Mount Sinai, 1 Gustave Levy Place, Box 1055, New York, N.Y. 10029. Phone number: 212-659-8554, Fax number: 212-241-4218. Email: emily.japp@mssm.edu.

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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 three 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 anti-hypertensive 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.

Introduction
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 three patients that presented in March 2020 to the Adrenal Center at the Mount Sinai Hospital in New York City with newly diagnosed pheochromocytomas. These three 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 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
three 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 (MRI) of the
abdomen with and without contrast, the adrenal mass measured 6.7 x 6 x 5 cm, and was
hypervascular without loss of signal.

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

Laboratory testing showed: elevated urine normetanephrine 2276 ug/24 h (122-676) with
normal urine metanephrine 158 ug/24 h (90-315). 24-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 seven 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 multi-gene 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 (HLRCC) 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 old. 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 two weeks and remained normotensive off any anti-hypertensive medications. In addition, her fasting glucose improved from 105 to 87 mg/dL. By six 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 four months. Computed tomography (CT) of the abdomen with contrast demonstrated a 6.3 x 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, that 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 two 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 ug/24 h (82-500) respectively, plasma and urine metanephrines 245 pg/mL (0-62) and 2076 ug/24 h (45-290) respectively, urine dopamine 1701 ug/24 h (0-510), urine epinephrine 102 ug/24 h (0-20), and urine norepinephrine 1631 ug/24 h (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 eight 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 four 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 multi-gene 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 six weeks after surgery, she had gained back eight 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 x 3.1 x 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 2-3 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
bowl obstruction and had three feet of necrotic bowel removed, which was complicated by a fistula that closed after seven months.

Laboratory testing in February 2020 showed: elevated plasma and urine normetanephrines 678 pg/mL (0-145) and 824 ug/24 h (82-500) respectively, and plasma and urine metanephrines 370 pg/mL (0-62) and 1564 ug/24 h (45-290) respectively. 24-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 (PET)-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 three weeks after surgery, she had gained back three pounds. Genetic testing was recommended but the patient deferred further evaluation.
Discussion

We herein present three 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 two-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 three 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 three 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, as compared to 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 as compared to 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 two 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 two 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 two 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 two 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 ACE-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 both Cases 1 and 3 (4). In addition, since these guidelines, a retrospective analysis comparing alpha-adrenergic with calcium channel blockade preoperatively showed that intraoperative hemodynamic instability was independent of the type of blockade (2). In all cases, regardless of the preoperative anti-hypertensive 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 three 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.

Data availability statement: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.
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| 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 x 6 x 5 cm                    | 6.3 x 4.8 cm                      | 4 x 3.1 x 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) |
|----------------------|--------------------------|---------------------------------------------------------------------|
| Plasma and/or urine normetanephrines | Urine: 2276 ug/24 h (122-676) | Plasma: 2418 pg/mL (0-145) Urine: 8610 ug/24 h (82-500) |
| Plasma and/or urine metanephrines | Urine: 158 ug/24 h (90-315) | Plasma: 245 pg/mL (0-62) Urine: 2076 ug/24 h (45-290) |
| Normetanephrine to metanephrine ratio | 14:1 (urine) | 10:1 (plasma) 4:1 (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. |
| Abbreviations: BP = blood pressure; HR = heart rate | | Preoperatively, maintenance on ramipril 2.5 mg daily, and initiation of amlodipine 2.5 mg daily. Underwent surgical adrenalectomy in July 2020. |