

Value of Systemic Hormonal Unloading in Pheochromocytoma



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ABSTRACT

Systemic unloading of adrenaline improves blood pressure (BP), but the effect on quality of life is not emphasized. This report aims to examine the outcome of systemic hormonal unloading through unilateral adrenalectomy in three pheochromocytoma cases.

Case 1 A 20-year-old male presented with anxiety, severe headaches, and BP 150/100 mmHg, taking terazosin and amlodipine. Stimulated bilateral adrenal venous sampling with glucagon stimulation (SBAVS-GS) showed predominant right adrenal secretion. Post right unilateral adrenalectomy, he is asymptomatic with the usual BP 110-120/60-70 mmHg without medication.

Case 2 A 51-year-old male presented with panic attacks, sweating, palpitations, headaches, and BP 220/110 mmHg, given terazosin and amlodipine. SBAVS-GS showed predominant right adrenal secretion. Post right unilateral adrenalectomy, he reported a reduction in his symptoms. His usual BP is 100-130/60-80 mmHg on low-dose amlodipine.

Case 3 A 27-year-old female presented with severe headache, dizziness, spontaneous epistaxis, palpitations, and BP 210/140 mmHg, taking bisoprolol, terazosin, and clonidine. SBAVS-GS showed predominant right adrenal secretion. Post right unilateral adrenalectomy, she had less headache and dizziness. Her BP is 110-140/70-90 mmHg on a single antihypertensive drug.

Conclusion Systemic hormonal unloading via unilateral adrenalectomy of the dominantly hormonal secreting adrenal gland is a good treatment option for pheochromocytoma; consequently, improving quality of life significantly.

Keywords Pheochromocytoma, Secondary hypertension, Systemic hormonal unloading, Adrenalectomy, Quality of life

INTRODUCTION

Pheochromocytomas are catecholamine-secreting tumors originating from the chromaffin cells of the adrenal medulla. On the other hand, paragangliomas are catecholamine-secreting tumors located in the sympathetic ganglia. These are rare tumors with an incidence of 0.2% to 0.6% among hypertensive patients.[1] A high clinical suspicion accompanied by extensive workup brings about its diagnosis.

The classic triad of pheochromocytoma is headache, sweating, and palpitations. The most common

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sign of pheochromocytoma is hypertension; but 5% of patients may be normotensive, usually associated with dopamine-secreting tumors.[1]

The prolonged exposure of myocytes, coronaries and cerebrovascular arteries to catecholamines has shown to increase the risk for myocardial infarction, angina pectoris, cerebrovascular accident, and transient ischemic attack.[2] If left untreated, it may lead to death. The definitive treatment is surgical removal of the hyperfunctioning dominant adrenal gland with adequate alpha-adrenergic blockade and calcium channel blockade preoperatively.

This case series aims to examine the outcome of systemic hormonal unloading through unilateral adrenalectomy in three pheochromocytoma cases.

METHODS AND RESULTS

This case series was done in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for writing and publication of this case series and the accompanying images (specimen images and histopathology slide image). This was also reviewed and approved by the Research Ethics Committee of University of Santo Tomas Hospital.

CASE 1 A 20-year-old male presented with BP of 150/100 mmHg, sweaty palms, anxiety, easy fatigability, dizziness, and frequent grade 3-6/10 throbbing occipital headaches that he banged his head to the wall with minimal relief of headache. His highest BP was 170/100 mmHg and his usual BP was 130-140/80 mmHg with maintenance medication of terazosin 5 mg/tab 1 tablet once a day (OD) and amlodipine 10 mg/tab 1 tablet OD. On physical exam, his BP was 130/80 mmHg, heart rate (HR) 80-90 bpm, height 170 cm, weight 90 kg, BMI 31.14, waist circumference 90 cm, with acanthosis nigricans, but no cushingoid features, no eye signs, no thyromegaly. He had a flabby abdomen and a normal neurologic exam.

His workup included: plasma renin activity 3.23 ng/ml/hr (N.V. 0.5-1.9 ng/ml/hr), 24-hour urine metanephrine 0.16 mg/24h (N.V. <1 mg/24h), and CT scan of the whole abdomen which showed a nodule on the apex of the left adrenal gland. Stimulated bilateral adrenal sampling with glucagon stimulation showed predominant secretion on the right (3489 pg/ml vs 2461 pg/ml).



Figure 1. Right adrenal gland. Grossly normal, measuring 3.0 x 2.0 x 1.0 centimeter.

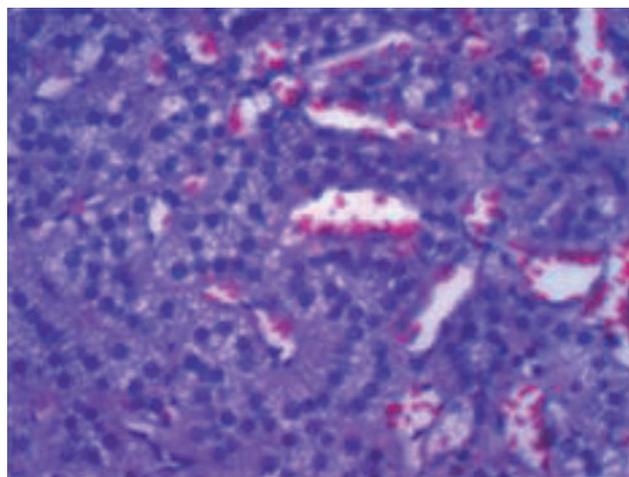


Figure 2. H&E staining of right adrenal cortex under HPO. Aggregate of neoplastic polyhedral cells in an alveolar pattern in the adrenal cortex.

He underwent right open unilateral adrenalectomy. The adrenal gland (Figure 1) appeared grossly normal with a size of 3.0 x 2.0 x 1.0 cm. On histopathology, there was a 0.1 cm adrenal cortical layer and a thin adrenal medulla that had a tan to dark brown, smooth, solid cut surfaces. There was an ill-defined lesion measuring 0.5 x 1.1 x 0.1 cm and with light brown smooth cut surfaces and areas of hemorrhages. Microsections (Figure 2) disclosed an inconspicuous aggregate of neoplastic polyhedral cells in alveolar pattern located in the adrenal cortex measuring 1.2 mm. These cells had round to ovoid nuclei, occasional prominent nucleoli, and finely granular amphophilic cytoplasm. The adrenal medulla grossly measured 0.15 cm. Microsections of the unremarkable medulla disclosed scattered

ganglion cells with anastomosing cords and trabeculae of chromaffin cells, which were separated by venous channels. The ganglion cells had round vesicular nuclei, occasional prominent nuclei, and abundant amphophilic cytoplasm. The chromaffin cells had round hyperchromatic nuclei, inconspicuous nucleoli, and abundant, finely granular, eosinophilic cytoplasm. The immunohistochemical staining showed synaptophysin positive, chromogranin and calretinin negative.

Post procedure, his lowest BP was 100/60 mmHg. On follow-ups, he is asymptomatic and his usual BP is 110-120/60-70 mmHg without any anti-hypertensive tablet.

CASE 2 A 51-year-old male presented with anxiety and panic attacks, sweating, palpitations, throbbing headaches, insomnia, family history of neurofibromatosis, and BP of 220/110 mmHg. His BP was controlled with terazosin 5 mg/tab 1 tablet OD and amlodipine 10 mg/tab 1 tablet OD. He has coronary artery disease and gastroesophageal reflux. He drank alcohol occasionally. One of his siblings had neurofibromatosis. He used to smoke for a total of 40 pack years. On physical exam, he was conscious, coherent, and anxious. His vital signs were as follows: BP 120/80 mmHg, HR 72 bpm regular. He had warm, moist skin, with multiple non-tender, soft, non-pigmented nodules approximately 2.0 x 2.0 cm on the left pre-auricular area, posterior and anterior aspect of left upper extremity, and anterior aspect of the right thigh. He had palmar erythema and clubbing of fingers on both hands. No eye signs such as exophthalmos, lid lag or proptosis. No thyromegaly. He had clear breath sounds. The cardiac exam showed a dynamic precordium, normal rate, regular rhythm, no murmurs, apex beat at the fifth LICS MCL. The abdomen was flabby, soft, and non-tender. The neurologic exam was normal.

A psychiatric consult and the following tests were performed: Hamilton anxiety rating scale (HAM-A) = 33, Hamilton rating scale (HAM-D) = 10 and Montgomery-Asberg depression rating scale (MADRS) = 23. He had anxiety and depression; hence, alprazolam was started.

His workup included: plasma renin activity 1.77 ng/ml/hr (N.V. 0.5-1.9 ng/ml/hr), 24-hour urine metanephrine 0.49 mg/24h (N.V. <1 mg/24h). CT scan of the whole abdomen showed 2.7 x 3.1 cm right adrenal nodule with peripheral enhancement.

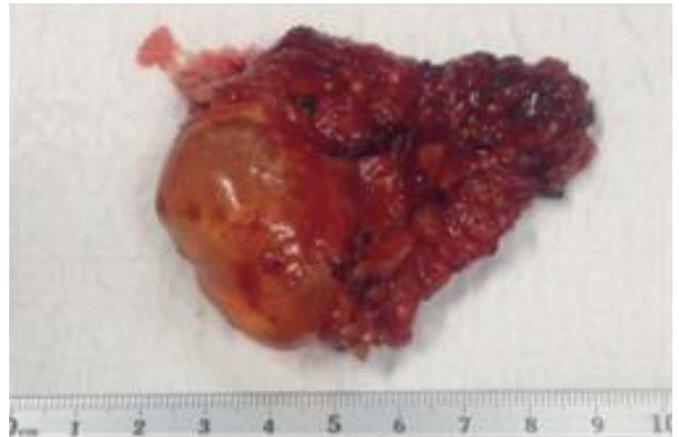


Figure 3. Right adrenal gland. 3.5 x 3.0 centimeter cystic mass containing golden-yellow fluid. (The mass is adherent to the adrenal tissue)

Stimulated bilateral adrenal sampling with glucagon stimulation showed predominant secretion on the right (5078 pg/ml vs 3139 pg/ml).

He underwent right open unilateral adrenalectomy. The right adrenal gland (Figure 3) was characterized as a 3.5 x 3.0 cm cystic mass containing golden-yellow fluid. The mass was adherent to the adrenal tissue. The histopathology showed an adrenal cyst. The adrenal medulla had clusters of ovoid cells with granular faintly basophilic cytoplasm. The immunohistochemical staining showed calretinin positive, synaptophysin and chromogranin negative.

Postoperatively, his lowest BP was 110/80 mmHg. He reported a significant reduction in his palpitation, headache, and no panic or anxiety attacks. A repeat psychiatric testing showed improvement in the degree of his anxiety and depression: HAM-A of 9 from 33, HAM-D of 14 from 10 and MADRS of 9 from 23. His usual BP range was 100-130/60-80 mmHg with only amlodipine 5 mg/tab 1 tablet OD. On follow-ups, his vital signs are BP 140/100 mmHg and HR 60 bpm regular. The cardiopulmonary and gastrointestinal examinations were unremarkable. The cranial nerves were intact.

CASE 3 A 27-year-old female presented with elevated BP (highest BP 210/140 mmHg) accompanied by graded 9-10/10 severe piercing frontal headache, dizziness, nausea, vomiting, spontaneous epistaxis, palpitations, and unintentional weight loss. Her antihypertensive medications were bisoprolol 2.5 mg/tab 1 tablet OD and terazosin 1 mg/tab 1 tablet OD and clonidine 75 mcg/tab 1 tablet PRN. She has a history of transient ischemic attack.

Her workup included: plasma renin 9.93 ng/mL/hr (N.V. 0.5-1.9), plasma aldosterone 45.28 ng/dL (N.V. 4-31), and 24-hour urine metanephrine 0.74 mg/24h (N.V. <1 mg/24h). Stimulated bilateral adrenal sampling with glucagon stimulation showed predominant secretion on the right (4975 pg/ml vs 3421 pg/ml).

She underwent right laparoscopic adrenalectomy. The right adrenal gland measured 5.5 x 3.5 x 0.3 cm. The histopathology showed adrenal medullary hyperplasia. The immunohistochemical staining showed chromogranin positive, calretinin and synaptophysin negative.

Post procedure, her lowest BP was 110/70 mmHg; she had less headache and dizziness. Her maintaining BP is 110-140/70-90 mmHg on amlodipine 5 mg/tab 1 tablet BID; there was no recurrence of headaches.

DISCUSSION

The symptoms of our patients were consistent with pheochromocytoma. These manifestations are products of catecholamines on various receptors of the body. Catecholamines work on the α_1 and α_2 receptors resulting in vasoconstriction and secretion of sweat glands leading to pallor and diaphoresis, respectively. Vasoconstriction effect of the α_1 and α_2 receptors can also increase BP while the effect on β_2 receptors is vasodilation.[1] The combination of the two effects can affect the sympathetic reflex leading to orthostatic hypotension. In the brain, the catecholamines on the α_1 and dopamine1 receptors can produce vasoconstriction; subsequently, resulting in a headache. The effect of catecholamines on the β_1 receptors in the kidneys is increased renin secretion.[3] The increased renin production can stimulate the renin-angiotensin-aldosterone pathway contributing to hypertension as well.[1] The palpitations, tachycardia, and angina can be attributable to the effect of catecholamine in the β_1 , β_2 and dopamine1 receptors that can increase the rate, contractility, automaticity, and conduction velocity of the heart.[4]

Among the many clinical manifestations of pheochromocytoma, hypertension (80.7%) was reported to be the most sensitive symptom, closely followed by headache (60.4%), palpitation (59.3%), and diaphoresis (52.4%). The triad of pheochromocytoma (58%) is also sensitive but presents in only a few patients.[5] Truly, there is no single clinical finding

that can define pheochromocytoma, but a good clinical judgment accompanied by thorough workup is necessary.

The diagnosis of a clinically suspected case of pheochromocytoma is confirmed by the following workup: 24-hour urine metanephrine, plasma catecholamines, bilateral adrenal vein sampling, and CT scan of the abdomen to localize the tumor. The 24-hour urine metanephrine has been widely used as a screening test. Urinary catecholamines provide good sensitivity (97%) as well as high specificity (99%). In spite of the high sensitivity and specificity, in a small number of patients, it can be normal. If it is a small tumor, it is more likely to release unmetabolized catecholamines due to a more rapid turnover rate giving normal values of catecholamine metabolites. Plasma and urinary catecholamines can be normal in episodically secreting tumors when measured between paroxysmal attacks, also in the presence of so-called non-functional or silent tumors.[6] These are the possible reasons why our patients had normal 24-hour urine metanephrine.

In a study by Asis, et al. [7], it showed the value of bilateral adrenal vein sampling (BAVS) with glucagon stimulation to clinch the diagnosis of pheochromocytoma and localize the small tumor. Among the 41 participants, 20 were diagnosed with unilateral pheochromocytoma; 16 were suspected of bilateral adrenal hyperplasia; the remaining 5 patients were considered normal. The study proved that BAVS with glucagon stimulation was a safe and effective tool to diagnose pheochromocytoma. In BAVS, the use of the glucagon test to establish a positive result depends on the significant increase in plasma concentrations of norepinephrine within 3 minutes of an intravenous bolus injection of glucagon. This evoked release appears dependent on the presence of the glucagon receptor.[8]

In a long-term follow-up study among pheochromocytoma patients, it was noted that they have higher cardiovascular events compared to patients with essential hypertension. The excess event rate is attributable to the prolonged exposure to the toxic effects of tumoral catecholamines.[3]

If the pheochromocytoma is left untreated, this could be detrimental to the patient's health. The prolonged exposure to catecholamines results in sustained hypertension, myocarditis, cardiomyopathy, lethal arrhythmias, impaired glucose tolerance, overt diabetes mellitus, organ ischemia, and se-

vere organ dysfunction.[9,10] The debate goes on if these effects are reversible or not. Some say that the cardiomyopathy may be reversible, but the study of Ferreira proved that there was an increased incidence of focal myocardial fibrosis in both newly and previously diagnosed cases of pheochromocytoma. Moreover, it implied that the damage persisted even after definitive surgical treatment.[11]

Here lies the value of systemic hormonal unloading. Systemic hormonal unloading is the process of unburdening the human body system of excess circulating catecholamines. This leads to complete restoration of organ function and/or improvement in the quality of life.

In cases where bilateral adrenal glands are hyperfunctioning, once the dominantly secreting adrenal gland has been localized through careful and precise bilateral adrenal vein sampling, unilateral adrenalectomy can be done to unload the system of excess catecholamines. The study of Malong, et al. proved that BAVS with glucagon stimulation is a valuable tool that localizes the dominantly secreting adrenal gland that can be surgically removed in

patients with bilateral pheochromocytoma. This not only alleviates chronic hypertension but also stops the progression of cardiometabolic complications. [8] giving patients a brighter and healthier future.

A study of Zhou, et al. [12], recommended that surgical management should aim at the improvement of life quality in MEN1 and prevention of fetal tumors in MEN2.

The strength of this study lies in the good judgment of the medical team in managing these cases to undergo BAVS and proceed with unilateral adrenalectomy for the purpose of unloading the system of the harmful effects of excessive catecholamines. The limitation of this study is the lack of a tool to measure qualitatively and quantitatively the quality of life pre and post-surgery for pheochromocytoma patients.

In conclusion, this case series has emphasized the importance of systemic hormonal unloading via unilateral adrenalectomy of the dominant adrenal in pheochromocytoma patients that results not in improved BP control, but more importantly, a better quality of life.

REFERENCES

1. Zuber SM, Kantorovich V, Pacak K. Hypertension in pheochromocytoma: characteristics and treatment. *Endocrinol Metab Clin North Am*. 2011;40(2):295–311.
2. Stolk RF, Mulder J, Timmers HJLM, Lenders JWM. Is the excess cardiovascular morbidity in pheochromocytoma related to blood pressure or to catecholamines? *JCEM*. 2013;98(3):1100–6.
3. Vetter H, Vetter W, Warnholz C, Bayer JM, Käser H, Vielhaber K, et al. Renin and aldosterone secretion in pheochromocytoma. Effect of chronic alpha-adrenergic receptor blockade. *Am J Med*. 1976;60(6):866–71.
4. Mercado-Asis LB, Siao RM, Amba NF. Evolving clinical presentation and assessment of pheochromocytoma: a review. *JMUST*. 2017;1:5–22.
5. Soltani A, Pourian M, Davani B. Does this patient have pheochromocytoma? a systematic review of clinical signs and symptoms, *J Diabetes Metab Disord*. 2016;15:6:1–12.
6. Zianni D, Tzanela M, Klimpoulos S, Thalassinou NC. Symptomatic pheochromocytoma with normal urinary catecholamine metabolites. *Hormones*. 2004;3(2):132–7.
7. Mercado-Asis LB, Tingtungco AG, Bolong DT, Lopez RA, Caguioa EV, Yamamoto ME, et al. Diagnosis of small adrenal pheochromocytoma by adrenal venous sampling with glucagon stimulation test. *Int J of Endocrinol Metab*. 2011(9):323–9.
8. Malong CLP, Tanchee-Ngo MJ, Torres-Salvador P, et al. Removal of dominant adrenal lateralized by glucagon-stimulated adrenal venous sampling alleviates hypertension in bilateral pheochromocytoma. *Journal of Life Sciences*. 2013;7(6):116–21.
9. Brouwers FM, Eisenhofer G, Lenders JW, et al. Emergencies caused by pheochromocytoma, neuroblastoma or ganglioneuroma. *Endocrinol Metab Clin North Am*. 2006;35:699–724.
10. Pacak K. Pheochromocytoma resection: the rule of surgical divergence. *AACE Clinical Case Reports*. 2016;2(1):e78–9.
11. Ferreira VM, Marcelino M, Piechnik SK, Marini C, Karamitsos TD, Ntusi NAB, et al. Pheochromocytoma is characterized by catecholamine-mediated myocarditis, focal and diffuse myocardial fibrosis, and myocardial dysfunction. *J Am Coll Cardiol*. 2016;67(20):2364–74.
12. Zhou GW, Wei Y, Chen X, Jiang XH, Li XY, Ning G, et al. Diagnosis and surgical treatment of multiple endocrine neoplasia. *Chin Med J (Engl)*. 2009;122(13):1495–500.



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