CASE REPORT

Cardiac Dopamine-Secreting Paraganglioma with Involved Skull Base and Retroperitoneum After a History of Pheochromocytoma Post Adrenalectomy

Chee Eng Hoo,1 MD, Chin-Sung Kuo,1 MD, Chun-Yang Huang,1,2 MD, Po-Hsun Huang,1,4 MD, An-Hang Yang,1,5 MD and Chiao-Po Hsu,1,2 MD

Summary

Cardiac paragangliomas are exceedingly rare. Herein, we describe a patient with a large dopamine-secreting cardiac paraganglioma who had a history of pheochromocytoma after right adrenalectomy. The cardiac surgery was uneventful and without blood pressure fluctuations. The measurement of plasma-free metanephrines or urinary fractionated metanephrines is used as an initial screening test for pheochromocytoma or paraganglioma detection. However, these results must be combined with those of a plasma 3-methoxytyramine test to accurately establish the rare dopaminergic phenotype of pheochromocytomas or paragangliomas, if suspected. F-FDOPA (6-[18F]-L-fluoro-L-3,4-dihydroxyphenylalanine)-based positron emission tomography (PET) and PET-computed tomography are relatively sensitive and specific; therefore, these techniques are recommended for patients with pheochromocytomas or paragangliomas before operation or during postoperative follow-up.

Key words: Cardiac tumor, Neuroendocrine tumor

Chromaffin cells produce two histologically identical tumors, namely pheochromocytomas and paragangliomas; these tumors arise from the adrenal medulla and extra-adrenal paraganglia, respectively. Paragangliomas are of two subtypes, parasympathetic paragangliomas which are usually found in the head and neck, and sympathetic paragangliomas. Approximately 85% of sympathetic paragangliomas are located below the diaphragm, near the adrenal or renal area, around the organ of Zuckerkandl, or in the urinary bladder, whereas the remainder are found in the thorax and heart. Cardiac paragangliomas are categorized as a very rare type of sympathetic paraganglioma, accounting for less than 0.3% of mediastinal tumors. The clinical symptoms depend on the site of origin and functionality of the tumors. Functional tumors secrete catecholamine, which causes symptoms of catecholamine excess, including palpitation, diaphoresis, and headache. Nonfunctional tumors may present with symptoms that depend on the site of organ obstruction or compression.

Herein, we describe a patient with a rare, large dopamine-secreting cardiac paraganglioma associated with dyspnea, chest tightness, dizziness, palpitation, and light-headedness who had a history of right adrenal pheochromocytoma after right adrenalectomy. The results of an imaging study suggested that an extra-adrenal paraganglioma was involved in the left retroperitoneal para-aortic area and skull base, which has not been described in the literature thus far.

Case Report

A 63-year-old woman with progressive exertional dyspnea was referred to our hospital for further management of cardiac paraganglioma. She did not have a history of hereditary pheochromocytomas or paragangliomas. In 1997, she underwent right adrenalectomy for pheochromocytoma with refractory hypertension. The diagnosis was based on high levels of urinary epinephrine, norepinephrine, and excreted dopamine as well as the results of magnetic resonance imaging of the abdomen. The operation was uneventful. The concentration of urinary epinephrine and norepinephrine decreased immediately after the operation; however, the excreted dopamine level remained high. The patient was regularly followed up every 6 months. The urinary vanillylmandelic acid (VMA) and epinephrine levels were consistently within their normal ranges during follow-up; however, the norepinephrine level remained slightly high (> 100 μg/24 hours), and the dopamine level was twice the upper limit of the normal
CARDIAC PARAGANGLIOMA

Figure 1. Preoperative (left) and 2-week postoperative (right) CXR.

Table. Laboratory Data Related to the Tumor

| Date       | VMA (mg) | Epinephrine (0-24 μg/day) | Norepinephrine (10-80 μg/day) | Dopamine (138-540 μg/day) | Sample origin |
|------------|----------|---------------------------|-------------------------------|---------------------------|---------------|
| Pre-op     | 22.5     | 16.2                      | 1310.6                        | 1313                      | Urine         |
| 1998/09    | 14.5     | 19                        | 73                            | 981                       | Urine         |
| 1999/01    | 4.8      | 9                         | 72                            | 1019                      | Urine         |
| 1999/07    | 6.1      | 10                        | 61                            | 668                       | Urine         |
| 2004/11    | 4.7      | 3                         | 88                            | 804                       | Urine         |
| 2004/04    | 5.7      | <2                        | 121                           | 1424                      | Urine         |
| 2008/08    | 5.4      | <7                        | 100                           | 484                       | Urine         |
| 2009/06    | 5        | <8                        | 230                           | 1671                      | Urine         |
| 2012/01    | 5.6      | <2                        | 162                           | >1000                     | Urine         |
| 2012/09    | 4        | <2                        | 102                           | 749                       | Urine         |

Blood

Epinephrine: 15 pg/mL
(Supine: 10-67, random: < 140 pg/mL)
Norepinephrine: 652 pg/mL
(Supine: 95-446, random: < 1700 pg/mL)

2013/04 4.4 < 2 155.9 2009.2 Urine
2015/11 5.3 < 2 112.1 1217.5 Urine
2016/11 5 14.4 120.1 1266.2 Urine
2017/04 4.9 13.9 131.8 1805.9 Urine

urinary dopamine level (> 1000 μg/24 hours). The serum norepinephrine and epinephrine levels were normal, but the dopamine level was not examined (Table).

In 2014, abdominal computed tomography (CT) revealed the presence of a 1.6-cm nodule in the patient’s left para-aortic region. The patient was normotensive, and the mass did not exhibit any interval changes. Hence, intervention was not provided, and regular follow-up was suggested.

Four months ago, the patient complained of progressively aggravated dyspnea on exertion with chest tightness, dizziness, palpitation, and lightheadedness. She went to a local clinic for treatment; however, the treatment was ineffective. She subsequently went to a regional hospital for symptom management. A preoperative chest X-ray revealed cardiomegaly and pulmonary edema (Figure 1, left). Arrhythmia was not noted. An echocardiogram revealed multiple coronary artery fistulae feeding into the pulmonary artery (Figure 2). A coronary CT angiogram was arranged, and the results revealed a hypervascular mass measuring 70 × 50 × 25 mm³ on the left heart abutting the pulmonary trunk and aortic root. The left main (LM), proximal left anterior descending (LAD), and left circumflex (LCX) arteries were encased within the mass (Figure 3).

The patient was transferred to our hospital for further management. Coronary angiography revealed multiple coronary fistulae at the LAD, LCX, and right coronary arteries as well as tumor blush, which indicated paraganglioma (Figure 4). F-FDOPA (6-[18F]L-fluoro-L-3, 4-
The induction of anesthesia was uneventful without alpha blockade. The patient underwent median sternotomy and was placed on cardiopulmonary bypass (CPB). During 334 and 223 minutes of CPB and aortic clamp, respectively, the tumor and LM artery were completely resected after transection of the ascending aorta and main pulmonary trunk (Figure 6). The LM orifice was ligated. The great saphenous vein was harvested to bypass the proximal aorta to the proximal LAD and LCX, separately. The aorta and pulmonary trunk were subsequently reconnected. The patient was weaned off CPB smoothly. Blood pressure fluctuation did not occur during the operation. The postoperative course was uneventful (Figure 1, right).

The tumor cells were positive for synaptophysin and succinate dehydrogenase complex subunits A and B. Sustentacular cells were highlighted using S-100 staining. The Ki-67 labeling index was < 2%. The tumor was well encapsulated without local invasion (Figure 7).

The final pathological diagnosis was a dopamine-secreting cardiac paraganglioma with involvement of the skull base and retroperitoneum. Long-term follow-up was suggested.

**Discussion**

Herein, we describe a patient with a rare pheochromocytoma, secreting large amounts of catecholamines, mainly norepinephrine and relatively small amounts of epinephrine. Two decades after right adrenalectomy, a dopamine-secreting cardiac paraganglioma with the involvement of the skull base and retroperitoneum was once more noted. The patient did not have a family history of von Hippel-Lindau disease, multiple endocrine neoplasia type 2, or neurofibromatosis type 1. A patient with this combination of a norepinephrine-secreting pheochromocytoma and a dopamine-secreting cardiac paraganglioma has not been described in the literature thus far.

Measurements of only plasma-free normetanephrine and metanephrine may be sensitive tests for the diagnosis of pheochromocytoma or recurrence, but such tests may fail to detect tumors that predominantly produce dopamine. Such tumors are extremely rare and usually occur as extra-adrenal paragangliomas. The predominance of dopamine production and relatively low production of other catecholamines in such tumors is due to a deficiency of dopamine-β-hydroxylase, an enzyme that converts dopamine to norepinephrine, in the tumor cells. Patients with dopamine-secreting paragangliomas are often normotensive and do not exhibit the classical presentations of pheochromocytomas, namely headache, hypertension, and diaphoresis; consequently, these tumors are usually identified incidentally. The initial symptoms of our patient
were mainly dyspnea on exertion, chest tightness, dizziness, and mild palpitation. These symptoms might have been due to the mass effect and excess dopamine secretion. All the aforementioned symptoms disappeared after the operation.

The presence of multiple coronary artery fistulae, which are often observed in patients with cardiac paraganglioma, was noted in our patient. Coronary artery fistulae are usually formed because of high-flow blood vessels supplying the tumor, which commonly appear highly concentrated and dilated. However, neovascularization in pheochromocytomas and paragangliomas may be caused by increased production of dopamine and vascular endothelial growth factor.

After adrenalectomy, the urinary levels of VMA, norepinephrine, epinephrine, and dopamine were monitored instead of the plasma levels because the test for urinary levels has higher sensitivity and specificity than that for plasma levels. Urinary dopamine levels have previously received relatively less attention in clinical practice. Our patient’s urinary dopamine level was twice the upper limit of the normal range throughout her twenties, which ac-
18F-FDOPA PET-CT discloses increased uptake in the left retroperitoneal para-aortic (arrow) and left temporal bone (arrowhead) area besides intrapericardium.

Figure 5. 18F-FDOPA PET-CT discloses increased uptake in the left retroperitoneal para-aortic (arrow) and left temporal bone (arrowhead) area besides intrapericardium.

Figure 6. Gross picture of the mass.

cording to current clinical opinions, suggests the possibility of a dopamine-secreting paraganglioma. Additional imaging studies were not conducted to determine the cause at that time. A test for plasma 3-methoxytyramine has been developed, offering the highest diagnostic performance in laboratory diagnosis in the past decade. However, tests for plasma 3-methoxytyramine, normetanephrine, and metanephrine are not currently available in our hospital. Paraganglioma is a slow-growing tumor. In our patient, the large cardiac paraganglioma might have grown slowly over many years. Therefore, it is reasonable to suspect that paraganglioma may present 20 years after adrenalectomy.

The current US Endocrine Society guidelines recommend the measurement of plasma-free metanephrines or urinary fractionated metanephrines as initial screening tests for pheochromocytomas or paragangliomas. These results, combined with those of the plasma 3-methoxytyramine test, can be used to accurately identify the dopaminergic phenotype of a pheochromocytoma or paraganglioma. Furthermore, notably, urine dopamine levels should never be used in such diagnostic work because most of the dopamine present in mammalian urine is produced by renal cells, rendering this test unacceptable for the evaluation of pheochromocytomas and paragangliomas.

The current US Endocrine Society guidelines recommend the measurement of plasma-free metanephrines or urinary fractionated metanephrines as initial screening tests for pheochromocytomas or paragangliomas. These results, combined with those of the plasma 3-methoxytyramine test, can be used to accurately identify the dopaminergic phenotype of a pheochromocytoma or paraganglioma. Furthermore, notably, urine dopamine levels should never be used in such diagnostic work because most of the dopamine present in mammalian urine is produced by renal cells, rendering this test unacceptable for the evaluation of pheochromocytomas and paragangliomas.

A metaiodobenzylguanidine scan is a common tool for detecting pheochromocytomas, but it has a high false-negative rate for nonfunctional or dopamine-secreting paragangliomas. 18F-FDOPA PET and PET-CT are highly sensitive and specific techniques that can provide additional independent information for the diagnosis and localization of benign and malignant pheochromocytomas. Therefore, 18F-FDOPA PET-CT was used to evaluate our patient’s condition, and the results showed an increased uptake of 18F-FDOPA in the temporal bone.

The term “malignant paraganglioma” was abandoned in the 2017 WHO classifications and replaced with “metastatic paraganglioma.” A histological system to assess the biological aggressiveness of paraganglioma is not currently available. However, if paragangliomas are detected at nonchromaffin sites, such as the bones, brain, and lymph nodes, the tumors are reclassified as metastatic paragangliomas. In this case, the increased signal in the skull base or retroperitoneal para-aortic area could not prove that these sites were nonchromaffin sites. Additional observation is necessary. Furthermore, dopamine-secreting paragangliomas tend to have a higher malignancy rate than noradrenaline- and adrenaline-secreting tumors.
The surgical removal of a pheochromocytoma or paraganglioma does not imply a complete cure. Recurrence might be observed in up to 16% of patients, particularly in patients with familial pheochromocytomas or paragangliomas, right adrenal tumors, and extra-adrenal tumors. Thus, long-term monitoring is necessary for all patients, including those who are apparently cured. Hence, in our patient, although the cardiac paraganglioma was resected completely, long-term follow-up of biochemical tests and imaging is highly recommended.

Conclusion

The measurement of plasma-free metanephrines or urinary fractionated metanephrines is the initial screening test for pheochromocytomas or paragangliomas. These results, combined with those of the plasma 3-methoxytyramine test, can be used to accurately establish the dopaminergic phenotype of a pheochromocytoma or paraganglioma. 18F-FDOPA PET and PET-CT are suggested for patients with pheochromocytomas or paragangliomas before operation or during postoperative follow-up. Long-term observation is necessary for pheochromocytomas or paragangliomas of the dopaminergic phenotype after operation owing to a high malignancy rate.

Disclosure

Conflicts of interest: None.

References

1. Martucci VL, Emaminia A, del Rioceo J, et al. Succinate dehydrogenase gene mutations in cardiac paragangliomas. Am J Cardiol 2015; 115: 1753-9.
2. Eisenhofer G, Goldstein DS, Sullivan P, et al. Biochemical and clinical manifestations of dopamine-producing paragangliomas: Utility of plasma methoxytyramine. J Clin Endocrinol Metab 2005; 90: 2068-75.
3. Feldman JM, Blalock JA, Zern RT, et al. Deficiency of dopamine-beta-hydroxylase. A new mechanism for normotensive pheochromocytomas. Am J Clin Pathol 1979; 72: 175-85.
4. Proux C, Fossati P, Fontaine P, et al. Dopamine-secreting pheochromocytoma: An unrecognized entity? Classification of pheochromocytomas according to their type of secretion. Surgery 1986; 100: 1154-62.
5. Foo SH, Chan SP, Ananda V, Rajaisingam V. Dopamine-secreting pheochromocytomas and paragangliomas: Clinical features and management. Singapore Med J 2010; 51: e89-93.
6. Chen YY, Huang WC, Huang MH, Lu TM, Hsu CP. The intrapericardial paraganglioma presenting as ascites and hemopericardium with impending tamponade. Int Heart J 2018; 59: 664-7.
7. Lee CC, Chua S, Huang SC, Lee FY, Chung SY. Intrapericardial paraganglioma with intratumoral coronary arterial aneurysm and an arteriovenous fistula. J Am Soc Echocardiogr 2009; 22: 211-6.
8. Osina TE, Links TP, Dullaart RP, et al. Emerging role of
dopamine in neovascularization of pheochromocytoma and paraganglioma. FASEB J 2017; 31: 2226-40.
9. Favier J, Igaz P, Burnichon N, et al. Rationale for anti-angiogenic therapy in pheochromocytoma and paraganglioma. Endocr Pathol 2012; 23: 34-42.
10. Sawka AM, Jaeschke R, Singh RJ, Young WF Jr. A comparison of biochemical tests for pheochromocytoma: Measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. J Clin Endocrinol Metab 2003; 88: 553-8.
11. Rao D, Petitsch M, Prejbisz A, et al. Plasma methoxytyramine: Clinical utility with metanephrines for diagnosis of pheochromocytoma and paraganglioma. Eur J Endocrinol 2017; 177: 103-13.
12. Lenders JW, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014; 99: 1915-42.
13. Imani F, Agopian VG, Auerbach MS, et al. 18f-fdopa pet and pet/ct accurately localize pheochromocytomas. J Nucl Med 2009; 50: 513-9.
14. Kim KY, Kim JH, Hong AR, et al. Disentangling of malignancy from benign pheochromocytomas/paragangliomas. PLoS One 2016; 11: e0168413.
15. Poitier É, Thauvette D, Hogue JC. Management of exclusively dopamine-secreting abdominal pheochromocytomas. J Am Coll Surg 2013; 216: 340-6.
16. Amar L, Servais A, Gimenez-Roqueplo AP, Zinzindohoue F, Chatellier G, Piault PE. Year of diagnosis, features at presentation, and risk of recurrence in patients with pheochromocytoma or secreting paraganglioma. J Clin Endocrinol Metab 2005; 90: 2110-6.