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Mini-Review

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Dopamine-Secreting Pheochromocytoma and Paraganglioma

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Abbreviations: ACTH, adrenocorticotropic hormone; CgA, chromogranin A; CT, computed tomography; DBH, dopamine β-hydroxylase; FDG-PET, fluorodeoxyglucose–positron emission tomography; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; PET, positron emission tomography; PNMT, phenylethanolamine N-methyltransferase; PPGL, pheochromocytoma/paraganglioma; SDHB, succinate dehydrogenase subunit B; TH, tyrosine hydroxylase.

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Abstract

Predominantly or exclusively dopamine-secreting pheochromocytoma and paraganglioma are very rare. We report a 64-year-old woman with an adrenal incidentaloma. She was normotensive and had no symptoms of catecholamine excess. The 24-hour urine catecholamine level showed normal norepinephrine (122.9 μg/day), normal epinephrine (24.3 μg/day), and markedly elevated dopamine (148 212.4 μg/day). ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy revealed tumor uptake. After α-blockade as preoperative management, she successfully underwent laparoscopic left adrenalectomy and was finally diagnosed with an exclusively dopamine-secreting pheochromocytoma. The tumor was histologically comprised of small polygonal cells with high cellularity and was immunohistochemically positive for all 3 catecholamine-synthesizing enzymes: tyrosine hydroxylase (very weak), dopamine β-hydroxylase (heterogeneous), and phenylethanolamine N-methyltransferase (very weak). Electron microscopy revealed very few catecholamine-containing small vesicles with a few organelles, which reflected immature cells. No biochemical or imaging evidence of recurrence or metastasis were evident 1 year after the surgery. We conducted a literature search in

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the PubMed database. A total of 33 cases were collected. Our case had the second-highest 24-hour urinary dopamine excretion and was the first in which immunostaining for catecholamine synthase and electron microscopy were performed together. Histological findings in our case give a possible hypothesis that the mechanism underlying a dopamine-secreting pheochromocytoma is associated with immature catecholamine vesicles in which dopamine β-hydroxylase is localized, thus resulting in inhibited conversion from dopamine to norepinephrine. We also discuss the reasons for the lack of catecholamine excess symptoms, whether preoperative management of α-blockade is needed, and the association between the prognosis and genetic mutation, with an extensive literature review.

Key Words: pheochromocytoma, paraganglioma, dopamine, dopamine-secreting, immunohistochemistry, electron microscopy

Pheochromocytomas and paragangliomas (PPGL) are rare neuroendocrine tumors derived from chromaffin cells of the adrenal medulla and sympathetic paraganglia. PPGL usually secrete norepinephrine and/or epinephrine and are characterized by catecholamine excess symptoms, such as hypertension, headache, palpitations, and sweating [1]. A dopamine-secreting PPGL is a very rare subtype that predominantly or exclusively secretes dopamine but not norepinephrine or epinephrine. It has been characterized by a lack of catecholamine excess symptoms, large tumor size, extra-adrenal location, and high malignant potential. However, its etiology, the reason for the lack of catecholamine excess symptoms, the need for preoperative α-blockers, and the prognosis and association with a genetic mutation remain unclear. To our knowledge, this is the first case of an exclusively dopamine-secreting pheochromocytoma in which immunostaining of catecholamine synthetic enzymes and electron microscopy of tumor tissues were performed together. We also conducted a literature review on this rare subtype of PPGL.

Case Presentation

A 64-year-old woman with a history of chronic thyroiditis and no family history of endocrine disease was incidentally determined to have a left retroperitoneal mass on abdominal ultrasonography. A subsequent abdominal computed tomography (CT) scan revealed a 5.6 × 5.1 × 10.6 cm left adrenal tumor (10-50 Hounsfield Units of CT attenuation value), which showed marginal irregularity and an internal cystic structure (Fig. 1A). She was admitted to our hospital for further investigation of a suspected adrenocortical carcinoma.

On admission, she was normotensive and did not present with any catecholamine excess symptoms, such as headache, sweating, or palpitations. Serum cortisol, adrenocorticotrophic hormone (ACTH), aldosterone, dehydroepiandrosterone sulfate, and an overnight 1 mg dexamethasone suppression test indicated normal cortisol suppression. However, because both random urinary metanephrine (1500 μg/Cr [<159]) and normetanephrine (2020 μg/Cr [<574]) were elevated 3 times higher than the upper limit of the normal range, a left adrenal pheochromocytoma was suspected. Plasma epinephrine (60 pg/mL [<111]) and norepinephrine (60 pg/mL [<750]) were normal, but dopamine (870 pg/mL [<30]) was markedly elevated. The 24-hour urinary excretion assay revealed that normetanephrine (1.3 mg/day [<0.33]), metanephrine (1.3 mg/day [<0.19]), and homovanillic acid (61.2 mg/day [<6.3]) were elevated, and epinephrine (24.3 μg/ day [<41]) and norepinephrine (122.9 μg/day [<160]) were normal, whereas dopamine (148 212.4 μg/day [<1100]) was markedly elevated (Table 1). Magnetic resonance imaging (MRI) findings displayed diffusely heterogeneous with mixed high and low intensity in T1- and T2-weighted, with a large cystic lesion (Fig. 1B-1D). Both ^{123}I-MIBG scintigraphy and fluorodeoxyglucose–position emission tomography (FDG-PET) indicated accumulation consistent with the same tumor, respectively (Fig. 1E and 1F), and there were no obvious metastatic findings. Based on these findings, the diagnosis of exclusively dopamine-secreting pheochromocytoma was made preoperatively. Laparoscopic left adrenalectomy was performed after preoperative administration of saline (1 L/day) and an α-blocker (doxazosin 1.0 mg/day) for 7 days. No intraoperative or postoperative hemodynamic instability was noted. Histopathology revealed that the tumor was composed of small spindle-shaped cells with a high nuclear-cytoplasmic ratio. The cells were densely packed and arranged in a diffuse pattern. A pseudo-rosette arrangement was observed in a small portion. The tumor cells had infiltrated the capsular veins. These findings suggest a moderate risk of metastasis based on a Grading of Adrenal Pheochromocytoma and Paraganglioma (GAPP) score [2] of 6: pseudo-rosette arrangement (1 point), high

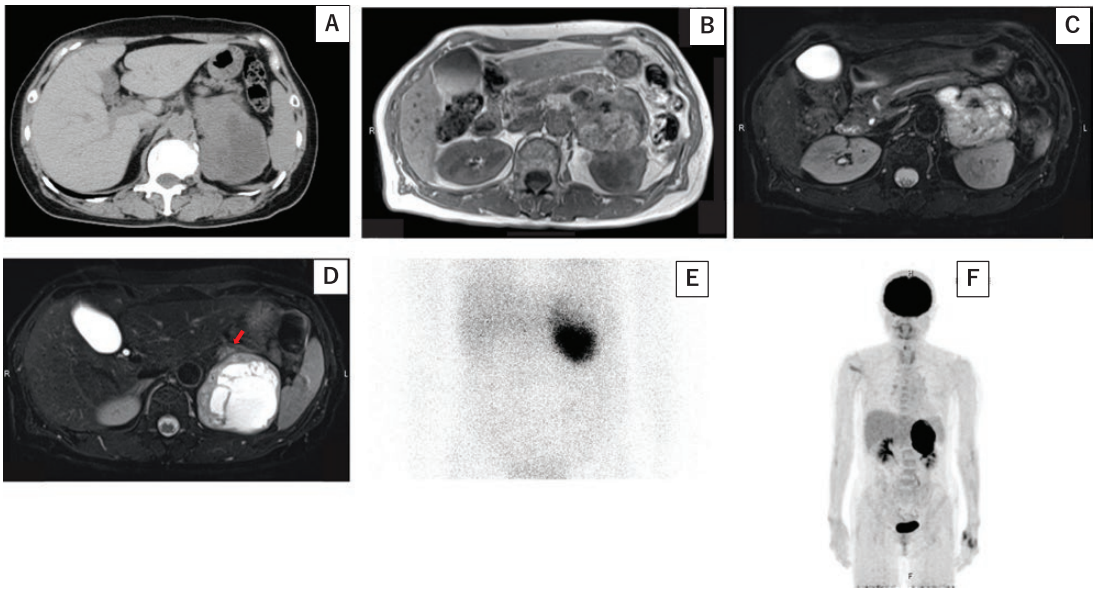

Figure 1. Diagnostic imaging: CT, MRI, ^{123}I-MIBG scintigraphy, and FDG-PET. A, CT scan shows left abdominal mass (5.6 × 5.1 × 10.6 cm). B, C, and D, MRI shows diffusely heterogenous with mixed high and low intensity on both T1- and T2-weighted. There is a large cystic lesion within the tumor that showed high signal with the same intensity as water on T2-weighted and a thinning normal adrenal gland (red arrow) on the ventral side of the tumor. E, ^{123}I-MIBG scintigraphy and F, FDG-PET indicate marked uptake into the tumor but no metastatic lesions.

cell density (2 points), vascular invasion (1 point), Ki-67 labeling index 7.5% (2 points), no comedo necrosis (0 points), and catecholamine type was adrenaline type (0 points). Chromogranin A (CgA) immunostaining was positive, and the final diagnosis was pheochromocytoma of the left adrenal gland. The immunostaining for succinate dehydrogenase subunit B (SDHB), which was performed to screen for hereditary PPGL syndrome, was positive and suggested negative for PPGL syndrome. Thus, no genetic examination was performed. No recurrence of the tumors was detected on a repeat PET-CT 6 months after the surgery. The patient is well and the catecholamine levels, including dopamine, are within normal ranges.

Literature Review

We performed a literature search on PubMed using the keywords "*dopamine*" AND "*pheochromocytoma*," "*dopamine*" AND "*paraganglioma*," "*dopamine-secreting*," and "*dopamine-producing*." All previous articles were limited to a single case report or case series, and we selected cases of predominantly or exclusively dopamine-secreting PPGL from 28 English articles. Units of 24-hour urinary catecholamines were converted from nmol/day to μg/day, and units for blood catecholamine concentrations were converted from nmol/L to pg/mL. We excluded 1 case in which only dopamine metabolites (homovanillic acid, methoxytyramine) were measured [3], and cases from 2 small case series [4, 5] in which detailed information about the cases was not available. The individual information is summarized in Table 2.

A total of 33 cases were collected [6-31]. The median age at the time of diagnosis was 48 years (range, 18-76 years), and the male to female ratio was 1:1.5. The most common symptoms were local discomfort and local pain due to tumor compression in 16 cases, and 8 cases in the neck region showed characteristic symptoms, such as tinnitus and hearing loss. Eleven of the 33 cases had nonspecific symptoms, such as weight loss, anorexia, anxiety, and diarrhea; 11 of the 33 cases had catecholamine excess symptoms, such as hypertension, headache, palpitations, and sweating, and 7 of the 33 cases were asymptomatic, as in the present case. The mean tumor size was 8.0 cm and 9.5 cm when located in the abdomen. MIBG scintigraphy was performed in 15 of the 33 cases and was positive in 11 of the 15 cases (^{131}I-MIBG 5 of 7 cases, ^{123}I-MIBG 6 of 8 cases). Treatment consisted of surgery in 21 cases, radiation therapy in 2 cases, and conservative therapy including chemotherapy

Table 1. Catecholamines and metabolites in 24-hour urinary excretion

	Preoperative	Postoperative (1 week after)	Normal range
Epinephrine (μg/day)	24.3	6.2	< 41
Norepinephrine (μg/day)	122.9	168.1	< 160
Dopamine (μg/day)	148212.4	799.6	< 1100
Metanephrine (mg/day)	1.3	0.10	<0.19
Normetanephrine (mg/day)	1.3	0.42	<0.33
Homovanillic acid (mg/day)	61.2	4.3	<6.3

Table 2. Literature review of dopamine-secreting PPGL of 33 cases (1983-2021)

Author [reference]	Year /sex	24-hour urinary excretion (μg/day)			Plasma concentration (pg/mL)			Location	Size (cm)	Symptoms	Treatment	Follow-up
		DA <400	NE <80	E <20	DA <30	NE <750	E <111					
Strauss 1983 [6]	23F	7700	[40]	[1.5]	-	-	-	Carotid	2.5	Blackout, palpitations, and tinnitus	Resection	18 months/No recurrence
Tripett 1986 [7]	42F	4420	[68]	[4]				Adrenal	NR	NR	Resection	NR/Liver metastasis
Ferrante 1995 [8]	56M				185	[547]	[55]	Adrenal	3	Headache, hypertension, sweating, and precordial pain	Resection	NR
Van Gelder 1995 [9]	54F	-	-	-	431	[172]	[42]	Para aortic	3	Dyspnea, retrosternal pain	Resection	6 months/No recurrence
Troughton 1997 [10]	40F	-	-	-	942	[381]	[19]	Jugular	NR	Anxiety, depression, flushes, palpitations, and hypertension	Radiation	NR
Levin 1998 [11]	48M		-	-	373	[428]	[45]	Para pharyngeal	7	Neck swelling	Resection	NR
Hirano 1998 [12]	76F	1451	[64.3]	[9.3]	703	[107]	[21]	Carotid bifurcation	3	Hypertension attack, headache, and vomiting	Resection	1 years/No recurrence
Yasunari 1999 [13]	65M	8000	-	-	280	[340]	[20]	Adrenal	NR	Chronic diarrhea, weight loss	Resection	NR
Taniguchi 2001 [14]	54M	9998	339	[17]				Adrenal	21	Epigastric discomfort, weight loss	Resection	2 years/ Metastasis
Koch 2003 [15]	40F				27942	1030	[15]	Carotid body	NR	Difficulties with swallowing, hoarseness, and hypotension	Resection	11 years / Extensive metastasis and died
Eisenhofer 2004 [16]	50M	[236]	[16]	[1.0]	600	[118]	[44]	Retroperitoneum	10	Abdominal pain, nausea, and dizziness	NR	Multiple lesion Retroperitoneum recurrence
Eisenhofer 2004 [16]	46M	478	124	[0.8]	776	[717]	[17]	Carotid Body and retroperitoneum	NR	Hoarseness, cough	NR	Recurrence
Eisenhofer 2004 [16]	34M	827	473	[2.4]	2092	2784	[12]	Pelvic	8	Deep vein thrombosis	NR	Metastasis
Eisenhofer 2004 [16]	20F	1374	410	[0.7]	2669	2229	[29]	Retroperitoneum	6	Nausea, vomiting, fishing, and hypertension	NR	Metastasis
Eisenhofer 2004 [16]	63F	1551	598	[6.0]	3705	5131	[57]	Retroperitoneum	10	Symptoms of Catecholamine excess hypertension	NR	NR
Eisenhofer 2004 [16]	38M	4802	1077	[2.0]	17749	14935	[106]	Neck, retroperitoneum	12	Neck pain, hypertension	NR	Extensive metastasis died
Eisenhofer 2004 [16]	48M	7291	123	[<1.0]	55619	6553	177	Retroperitoneum	9	Symptoms of Catecholamine excess	NR	Extensive metastasis died
Tam 2005 [17]	71F	12347.1	[37.2]	[6.4]	-	-	-	Retroperitoneum	10.4	Weight loss, low back pain	Resection	4 months/No recurrence Lung carcinoma occurred

Table 2. Continued

Author [reference]	Year /sex	24-hour urinary excretion (μg/day)			Plasma concentration (pg/mL)			Location	Size (cm)	Symptoms	Treatment	Follow-up
		DA <400	NE <80	E <20	DA <30	NE <750	E <111					
Dubois 2005 [18]	35F		normal	normal	459	normal	normal	Adrenal	12	Headache, nausea, sweating Vomiting and panic attacks	Resection	7 years/No recurrence
Jeffery 2007 [19]	61M	4682.7	[47.52]	[12.8]	-	-	-	Carotid body	NR	Hypertension, hypotension, syncope	Conservative	NR
Gangopadhyway 2008 [20]	70F	72063	[12.3]	[<4.5]	-	-	-	Near adrenal	28.7	Hypochondrial Pain, anorexia, nausea, and weight loss	Conservative	Died within a few weeks
Foo 2010 [21]	64F	391374	151.0	24.1	-	-	-	Para aortic	13	Abdominal swell Weight loss	Resection	1 months/ No recurrence
Eduardo 2011 [22]	71M				336	[266]	[18]	Jugular	NR	Hypertension, syncope, nausea, vomiting, headache, and vertigo	Conservative	4 months
Jin 2012 [23]	26F	1565.3	normal	normal	-	-	-	Adrenal	3.4	Asymptomatic	Resection	10 months/No recurrence
Soh 2012 [24]	62M	747.1	[37.71]	normal	-	-	-	Carotid body	5.3	Neck lump, hearing impairment giddiness, cough, and hoarseness	Radiation	3 years/Decrease in size of tumor after radiotherapy
Poirer 2013 [25]	63F	5775.6	normal	normal	-	-	-	Para adrenal	14	Hypochondrium pain, hypertension Worsened by respiration	Resection	3 months/No recurrence
Rajeev 2014 [26]	18F	1036	[67.92]	[7.41]				Adrenal	1	Asymptomatic	Resection	NR
Tuleasca 2016 [27]	62M				3134	normal	normal	Carotid body	4.7	Cervical mass pain, hypertension	Resection	30 months/ Recurrence
Matsuda 2016 [28]	70F	7933.2	102.2	[8.1]	-	-	-	Abdominal aorta	5	Asymptomatic	Resection	1 years/No recurrence
Tyler 2017 [29]	43F	6988	normal	normal	-	-	-	Adrenal	4	Asymptomatic	Resection	2 years/No recurrence
Zahraa 2019 [30]	36M	-	-	-	435	normal	normal	Bilateral carotid, jugular foreman, periaortic arch	2.5	Hypertension, tinnitus carotid mass	Resection	2 years/Recurrence
Jing 2021 [31]	28F	2265.9	normal	normal				Adrenal	7	Nausea, vomiting, abdominal pain, and palpitation	Resection	NR
Present case	54F	148212.4	122.9	24.3	870	[60]	[60]	Para adrenal	10.6	Asymptomatic	Resection	6 months/No recurrence

Abbreviations: DA, dopamine; E, epinephrine; F, female; M, male; NE, norepinephrine; NR, not recorded.

in 2 cases. Preoperative α-blockers were administered to 8 of 33 patients. The median follow-up time was 6 months, with recurrence or metastasis in 10 cases and mortality in 5 cases.

Discussion and Conclusions

PPGL is a rare endocrine tumor with an annual incidence of 0.6 per 100 000 people [32]. Among them, dopamine-secreting PPGL, which predominantly or exclusively secrete dopamine, is extremely rare. According to our literature search, only 33 cases including our case have been reported to date [6-31].

To explore the mechanisms for secreting dopamine predominantly or exclusively from a PPGL, we propose 2 hypotheses. First, it has long been considered that the lack of expression of dopamine β-hydroxylase (DBH) by the PPGL is responsible for a dopamine-secreting PPGL based on a report by Feldman et al [33]. This has led many authors to predict that dopamine-secreting PPGL is due to a deficiency in tumor DBH. However, according to our literature search, there was no dopamine-secreting PPGL case in which tumor DBH activity was measured for confirmation. Immunostaining with DBH antibodies was performed in 2 cases, which was found decreased staining [13, 28]. In the present case, we could not measure tumor DBH activity because the specimen was immediately formalin-fixed after tumor resection. We performed immunostaining for catecholamine synthase on the resected tumor tissue and determined faintly positive DBH expression in the tumor tissue, rather than a significant decrease in the expression of tyrosine hydroxylase (TH) or phenylethanolamine N-methyltransferase (PNMT) (Fig. 2c-2f). Then, to understand the reasons for secreting dopamine exclusively, we examined the electron microscopic findings to determine whether the tumor cells were mature enough for catecholamine synthesis and secretion. Scant cytoplasmic organelles were detected in the tumor cells, including the mitochondria and a few small dense vesicles about 100 nm in diameter, which were compatible with catecholamine vesicles (Fig. 2g-2h). Those vesicles were similar to those of neuroblastoma but more immature than those of the adult adrenal medulla or an ordinary pheochromocytoma. Although these tumor cells had catecholamine-synthesizing enzymes, the tumor cell structure was extremely immature. In general, TH and PNMT exist in the cytoplasmic fraction, and only DBH is located in a vesicle [34, 35]. Therefore, the immature catecholamine vesicles may cause the catecholamine biosynthetic pathway to stall at the conversion of dopamine to norepinephrine, thus resulting in excess production of dopamine compared to norepinephrine and epinephrine.

Second, it is also possible that loss-of-function mutations in the *DBH* gene and others that modulate DBH activity resulted in dopamine being secreted predominantly or exclusively from the PPGL. Excess aldosterone secretion from aldosterone-producing adrenal cortical adenomas is attributable to somatic mutations in ion channel genes, including *KCNJ5*, *CACNA1A*, *ATP1A1*, and *ATP2B3*, thereby resulting in constitutive activation of aldosterone synthase CYP11B2 [36]. In addition, excess cortisol secretion from cortisol-producing adrenal cortical adenomas is due to somatic mutations in *PRKACA*, thereby resulting in constitutive activation of ACTH action and cortisol-synthesizing enzymes [37]. Interestingly, an extremely rare primary autonomic failure, called norepinephrine

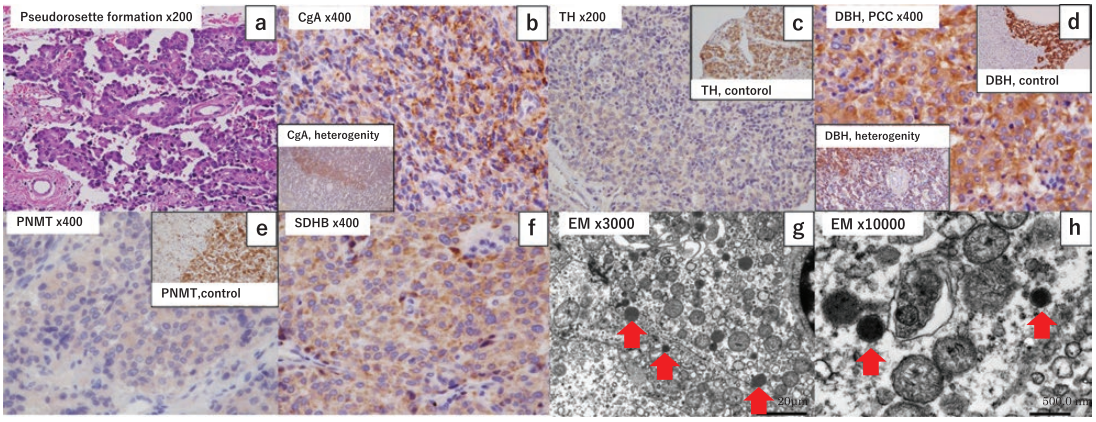

Figure 2. Microscopic findings. The hematoxylin and eosin–stained tumor cells were small, with spindle-shaped to round nuclei, a granular cytoplasm, a high N/C ratio, and high density. A small portion was arranged in a pseudo-rosette pattern (a). CgA was positive with heterogeneity (b). Compared with positive controls of normal adrenal medulla, TH was mostly negative (c), DBH was positive with heterogeneity (d), PNMT was mostly negative (e). SDHB was diffusely positive (f). EM showed that the tumor tissue contained small secretory granules with diameters of about 100 nm (g, h, red arrows). Abbreviations: CgA, chromogranin A; DBH, dopamine β-hydroxylase; EM, electron microscopy; N/C, nucleo-cytoplasmic, PCC, pheochromocytoma; PNMT, phenylethanolamine-N-methyltransferase; SDHB, succinate dehydrogenase subunit B; TH, tyrosine hydroxylase.

deficiency, presents with high plasma dopamine levels and no norepinephrine, which is caused by a somatic loss-of-function mutation in the *DBH* gene [38, 39]. These reports allowed us to propose another hypothesis that the mechanism of predominantly or exclusively dopamine-secreting PPGL is due to a somatic mutation in *DBH* or other genes that modulate DBH activity in the tumor.

Based on our immunohistochemical and electron microscopical data, the unique tumor histology of "immature catecholamine vesicles" may be associated with dopamine-secreting PPGL, but it remains to be elucidated in a future study whether mutations in *DBH* or other genes are also present.

The clinical symptoms of dopamine-secreting PPGL vary but are often nonspecific or due to tumor compression, and rarely present with typical catecholamine symptoms, such as sustained or paroxysmal hypertension (Table 2). This is probably due to the lower affinity of dopamine for the α and β receptors compared with norepinephrine and epinephrine. Dopamine has various dose-dependent hemodynamic effects; at low doses (< 5 μg/kg/min), dopamine has a vasodilatory effect and inhibits norepinephrine release via dopamine receptors; at moderate doses (5-15 μg/kg/min), dopamine has an inotropic effect via β adrenergic receptors, and at higher doses (> 15 μg/kg/min), it has a vasopressor effect by increasing peripheral vascular resistance via α adrenergic receptors [40]. According to a study on the relationship between the administered dopamine dose and plasma free dopamine concentrations in adults, even a low dose of dopamine (4 μg/kg/min) causes a rapid increase in plasma free dopamine concentration to more than 1000 times the upper normal limit (> 3.0×10^4 ng/L) [41]. Although plasma free dopamine concentration in our case (870 pg/mL) was much higher than normal, it was much lower than the concentration after a low-dose intravenous dopamine infusion, which does not have a vasopressor effect, explaining why this case was normotensive. Furthermore, the median plasma free dopamine concentration of 776 pg/mL in all 33 cases suggests that the secreting "dose" of dopamine from the tumor into the bloodstream in most dopamine-secreting PPGL cases remained in the low dose range, with effects only on dopamine receptors.

Diagnosing dopamine-secreting PPGL is challenging for clinicians. The lack of catecholamine excess symptoms makes it difficult to suspect the presence of PPGL, and most cases are incidentally discovered tumors due to nonspecific or local symptoms. Furthermore, a dopamine-secreting PPGL may be overlooked by measuring plasma or urinary fractionated metanephrine alone. In our case, the patient was asymptomatic and the tumor was found quite incidentally on an imaging study. The tumor was suspected to be an adrenocortical carcinoma due to its large size, low lipid content (CT attenuation values of 10-50), and lack of catecholamine symptoms. In general, pheochromocytomas and adrenocortical carcinomas cannot be discriminated by imaging findings alone [42]. In addition, a dopamine-secreting PPGL is larger (mean 8.0 cm, 9.5 cm when located in the abdomen) and tends to lack the typical symptoms of PPGL. This suggests that dopamine-secreting pheochromocytomas or near adrenal paragangliomas (as in the present case) have a greater potential risk to mimic an adrenocortical carcinoma than a normal PPGL. When clinicians encounter a large incidental adrenal or retroperitoneal tumor that does not present with catecholamine excess symptoms, a dopamine-secreting tumor should be listed in the differential diagnosis and screening tests for dopamine and its metabolites should be performed.

Standard treatment for dopamine-secreting PPGL is tumor resection, but it is unclear whether preoperative α-blockade is necessary. In 1 case series of 50 patients with pheochromocytoma, Proye et al reported on 3 patients who suffered circulatory collapse after preoperative α-blockade and presented with mixed dopamine secretion, suggesting that the circulatory collapse may have been caused by the enhanced vasodilatory effect of the α-blockade [4]. However, in the present series, 4 [8, 18, 26, 31] of 8 patients who received α-blockers had prolonged hypotension, but no case developed circulatory collapse, and 4 cases had no adverse events, including hypotension. Prolonged hypotension in cases of PPGL is usually caused by chronic dehydration and rapid catecholamine withdrawal [43], and it is a common complication, not only in dopamine-secreting PPGL. Furthermore, prolonged hypotension occurs even in a patient who do not receive α-blockers [21]. One study reported that high urinary dopamine levels are an independent predictor of prolonged intraoperative hypotension [44]. These findings suggest that hypotension in patients with a dopamine-secreting PPGL may not necessarily be due to preoperative α-blockade. In addition, intraoperative hypertensive events were reported in 4 of 33 cases [8, 12, 21, 31], of whom 2 cases [12, 21] did not receive preoperative α-blockade. Dopamine has a lower affinity for α and β receptors than norepinephrine and epinephrine, so hypersecretion is less likely to lead to excess catecholamine symptoms, such as tachycardia and hypertension. However, considering that the exocytic secretion of catecholamines in PPGL is episodic and occasionally undetectable [34], the ability to overproduce norepinephrine and epinephrine is not always lost even in predominantly or exclusively dopamine-secreting PPGL, as shown by the high urine and blood levels of metanephrine and normetanephrine in our case. A marked increase in blood-free norepinephrine levels was observed during intraoperative hypertension in 1 case [8], suggesting that even dopamine-secreting tumors can be a potential source of norepinephrine and epinephrine. For these reasons, we recommend preoperative

management with α-blockade and hydration for patients with dopamine-secreting PPGL.

In summary, we present a case of an exclusively dopamine-secreting pheochromocytoma. The clinical course of the present case highlights the potential risk of dopamine-secreting pheochromocytoma being mimicked as an adrenocortical carcinoma due to its size, imaging findings, lack of catecholamine symptoms, and the importance of performing biochemical tests that include dopamine. After an extensive literature review, plasma free dopamine does not reach levels that act on α and β receptors in most dopamine-secreting PPGL cases and this is the probable reason for the lack of catecholamine symptoms. Because an intraoperative hypertensive crisis has been reported in some dopamine-secreting PPGL cases, preoperative α-blockade should be considered. Although a genetic analysis in dopamine-secreting tumor tissue may provide additional insight into the dopamine-secreting phenotype in the future, histological findings in our case show that the mechanism of dopamine-secreting PPGL can be associated with "immature catecholamine vesicles" in which DBH is localized, thus resulting in inhibited conversion from dopamine to norepinephrine.

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