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Case Report

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Mixed Corticomedullary Tumor Accompanied by Unilateral Aldosterone-Producing Adrenocortical Micronodules: A Case Report

Sawa Yoshida,[1] Naru Babaya,[1] Hiroyuki Ito,[1] Yoshihisa Hiromine,[1] Yasunori Taketomo,[1] Fumimaru Niwano,[1] Shuzo Imamura,[1] Yuto Yamazaki,[2] Hironobu Sasano,[2] Yumiko Kawabata,[1] Shinsuke Noso,[1] and Hiroshi Ikegami[1]

[1]Department of Endocrinology, Metabolism and Diabetes, Kindai University Faculty of Medicine, Osaka 589-8511, Japan; and [2]Department of Pathology, Tohoku University Graduate School of Medicine, Miyagi 980-8575, Japan

ORCiD numbers: 0000-0002-3538-9779 (S. Yoshida); 0000-0003-2466-1228 (N. Babaya); 0000-0001-7634-1424 (H. Ito); 0000-0002-7317-236X (Y. Hiromine); 0000-0003-1366-2049 (Y. Taketomo); 0000-0003-4673-9401 (F. Niwano); 0000-0002-6600-8641 (H. Sasano); 0000-0003-4239-7942 (Y. Kawabata); 0000-0002-0943-8450 (S. Noso); 0000-0001-8808-4605 (H. Ikegami).

Abbreviations: ACTH, adrenocorticotropin; CT, computed tomography; CYP11β2, 18-hydroxylase aldosterone synthase; MCMT, mixed corticomedullary tumor; ref., reference value.

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Abstract

Mixed corticomedullary tumors (MCMTs) are rare and comprise medullary and cortical cells in a single adrenal tumor. The mechanisms underlying their development have not been fully elucidated. Here, we report a case of MCMT in a 42-year-old woman. Based on the preoperative clinical findings, the patient was diagnosed as having a pheochromocytoma with subclinical Cushing syndrome. Postoperative pathological diagnosis revealed that the tumor demonstrated morphologically distinct medullary and cortical components, which produced catecholamines and cortisol, respectively. Hybrid tumor cells producing both catecholamines and cortisol were not detected. Adrenocorticotropin (ACTH)-positive tumor cells were identified to be present in the pheochromocytoma. This ectopic production of ACTH can contribute to an autonomous cortisol production in a paracrine manner. In addition, micronodules producing aldosterone were detected in the adrenal tissue adjacent to the tumor. The simultaneous development of these 2 lesions may not be correlated with each other; however, this case confirms the importance of a detailed histopathological examination of the adrenal lesions harboring complicated hormonal abnormalities by providing pivotal and indispensable information on their pathogenesis and the possible interaction of the hormones produced in the adrenal gland.

Key Words: adrenal glands, mixed corticomedullary tumor, composite pheochromocytoma, subclinical Cushing syndrome, aldosterone-producing micronodules

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Mixed corticomedullary tumors (MCMTs) are composed of medullary and cortical cells in a single adrenal tumor [1], which can produce catecholamines, cortisol, or both [2]. MCMTs are extremely rare because the adrenal medulla and cortex have different embryological origins, namely, the neuroectoderm and mesoderm, respectively. To the best of our knowledge, approximately 30 cases have been reported in the English literature [1-11]. Therefore, the pathogenesis of this interesting but rare disorder remains unknown.

Here, we report a rare case of an MCMT consisting of pheochromocytoma and cortisol-producing tumor, in which aldosterone-producing cortical micronodules were histologically detected in the nonneoplastic adrenal gland adjacent to the tumor. A simultaneous occurrence of pheochromocytoma and primary aldosteronism is very rare, as only 9 cases have been reported to the best of our knowledge [12, 13]. In addition, MCMT accompanied by aldosterone-producing micronodules, as in this case, has not been reported in earlier studies. The combination of these lesions could result in a state of excess production of 3 adrenal hormones (catecholamines, cortisol, and aldosterone) in the same patient. In addition, we discuss the origin of the MCMT and the possible correlation between pheochromocytoma, cortisol-producing adenoma, and hyperaldosteronism.

Case Presentation

A 42-year-old woman was referred to our hospital to evaluate a large right adrenal mass. The patient had been healthy until 4 months earlier, when she started experiencing headaches, hyperhidrosis, and thirst. She was diagnosed with hypertension and type 2 diabetes by a general practitioner. She was then treated with a calcium channel blocker for hypertension and a dipeptidyl peptidase-4 inhibitor for type 2 diabetes. However, her symptoms did not improve; therefore, she was referred to a nearby hospital, where her antidiabetic medication was changed to insulin therapy. An abdominal computed tomography (CT) scan revealed a mass in the right adrenal region.

Subsequently, she was referred to and admitted to our hospital for further examination. On admission, there were no signs or symptoms of excess adrenal cortical hormones. She experienced a headache, hyperhidrosis, and a weight loss of approximately 10 kg during the 4 months before admission. Blood pressure was maintained within the normal range using an antihypertensive drug (amlodipine besilate, 2.5 mg/day). Her past medical history was unremarkable; her family history revealed diabetes and hypertension in her father and mother, respectively. Her clinical parameters were as follows: body height, 166.5 cm; body weight, 53.4 kg; blood pressure, 128/70 mm Hg; and heart rate, 80 beats/minute. Laboratory data are summarized in Table 1. Complete blood count and biochemistry test results were all within the normal range, except for diabetes-related indicators (fasting blood glucose, 147 mg/dL; glycated hemoglobin A_{1c}, 8.5%).

Endocrinological examination revealed markedly increased plasma and urine catecholamine levels, especially norepinephrine (5084 pg/mL in the plasma [reference value (ref.) 100-450 pg/mL] and 1816 μg/day in the urine [ref. 48.6-168.4 μg/day]) and its metabolite normetanephrine (80.55 mg/day in the urine [ref. 0.09-0.33 mg/day]). Plasma aldosterone concentration, plasma renin activity, and aldosterone/renin ratio were 211 pg/mL (ref. 29.9-159 pg/mL), 1.2 ng/mL/h (ref. 0.3-2.9 ng/mL/h), and 175 (pg/mL)/(ng/mL/h) (ref. < 200 [pg/mL]/[ng/mL/h]), respectively. Urine aldosterone level (21 μg/day [ref. 0-10 μg/day]) was also elevated; however, this was measured under conditions where renin was not suppressed. Early morning cortisol and adrenocorticotropin (ACTH) levels were almost within normal limits (14.6 μg/dL [ref. 6.2-19.4 μg/dL] and 7.1 pg/mL [ref. 7.2-63.3 pg/mL], respectively). However, 24-hour urine free-cortisol (294 μg/day [ref. 11.2-80.3 μg/day]) was elevated (cortisol and ACTH levels were measured using Eclusys Cortisol II and Eclusys ACTH [Roche Diagnostics Inc]). In addition, cortisol and ACTH levels at 12:00, 18:00, and 23:00 h were 12.5, 14.1, 12.8 μg/dL and 5.3, 7.7, 6.2 pg/mL, respectively, suggesting that diurnal variations in ACTH and cortisol were absent. The plasma cortisol level in the overnight 1 mg dexamethasone suppression test was 11.7 μg/dL (ref. < 5 μg/dL), indicating an autonomous secretion of cortisol.

Plain abdominal CT scan revealed a round, heterogeneous mass measuring 10.7 × 10.3 cm on the right adrenal gland (Fig. 1A). Magnetic resonance imaging on T2-weighted images demonstrated a heterogeneous, high-intensity lesion containing encapsulated fluid lesions in the right adrenal gland (Fig. 1B). ^{123}I-metaiodobenzylguanidine scintigraphy revealed a high uptake in the tumor area, but no uptake in other areas (Fig. 1C).

The patient underwent right adrenalectomy. The right adrenal gland and adjacent periglandular adipose tissue weighed 780 g. Macroscopic examination revealed a brown encapsulated tumor, measuring 11.8 × 11.3 × 11.4 cm.

Histologically, the tumor demonstrated 2 morphologically distinct components: the medullary and cortical components (Fig. 2A-2I). The tumor cells in the medullary component were immunohistochemically positive for tyrosine hydroxylase, chromogranin A, and synaptophysin (Fig. 2C-2E). Based on these histological findings and blood data, the tumor was diagnosed as pheochromocytoma. The cells in the cortical component were immunohistochemically positive for 17α-hydroxylase, 11β-hydroxylase (CYP11β1), and steroidogenic factor-1 (Fig. 2G-2I) and negative for

Table 1. Laboratory findings of the patient

Peripheral blood			**Endocrinological data**			
WBC	7900/mm^3	(3300-8600)	(Plasma)			
RBC	462 × 10^4/mm^3	(386-492)	Epinephrine		78 pg/mL	(0-100)
Hb	14.0 g/dL	(11.6-14.8)	Norepinephrine		5084 pg/mL	(100-450)
Ht	43.3%	(35.1-44.4)	Dopamine		44 pg/mL	(0-20)
Plt	30.5 × 10^4/mm^3	(15.8-34.8)	Renin activity		1.2 ng/mL/h	(0.3-2.9)
			Aldosterone		211 pg/mL	(29.9-159)
Biochemical data			ARR		175	(< 200)
T.P.	6.6 g/dL	(6.6-8.1)	ACTH	(06:00)	7.1 pg/mL	(7.2-63.3)
Albumin	4.2 g/dL	(4.1-5.1)		(12:00)	5.3 pg/mL	
T.Bil	0.9 mg/dL	(0.4-1.5)		(18:00)	7.7 pg/mL	
AST	13 U/L	(13-30)		(24:00)	6.2 pg/mL	
ALT	22 U/L	(7-23)	Cortisol	(06:00)	14.6 μg/dL	(6.2-19.4)
LDH	195 U/L	(124-222)		(12:00)	12.5 μg/dL	
ALP	207 U/L	(106-322)		(18:00)	14.1 μg/dL	
rGTP	28 U/L	(9-32)		(24:00)	12.8 μg/dL	
BUN	13 mg/dL	(8-20)	DHEA-S		9 μg/dL	(19-231)
Crea	0.72 mg/dL	(0.46-0.79)	(Urine)			
Na	142 mEq/L	(138-145)	Epinephrine		39.3 μg/day	(3.4-26.9)
K	4.4 mEq/L	(3.6-4.8)	Norepinephrine		1816.0 μg/day	(48.6-168.4)
Cl	103 mEq/L	(101-108)	Dopamine		829.0 μg/day	(365-961.5)
Glucose	147 mg/dL	(73-109)	Metanephrine		1.55 mg/day	(0.04-0.19)
T.chol	213 mg/dL	(142-220)	Normetanephrine		80.55 mg/day	(0.09-0.33)
HbA_{1c}	8.5%	(4.9-6.2)	Aldosterone		21 μg/day	(0-10)
			Cortisol		294 μg/day	(11.2-80.3)

Reference ranges are in parentheses.

Abbreviations: ACTH, adrenocorticotropin; ALP, alkaline phosphatase; ALT, alanine transferase; ARR, aldosterone/renin ratio; AST, aspartate transaminase; BUN, blood urea nitrogen; Cl, chlorine; Crea, creatinine; DHEA-S, dehydroepiandrosterone-sulfate; Hb, hemoglobin; HbA_{1c}, glycated hemoglobin A_{1c}; Ht, hematocrit; K, potassium; LDH, lactate dehydrogenase; Na, natrium; Plt, platelets; RBC, red blood cells; rGTP, gamma-glutamyl transferase; T.Bil, total bilirubin; T.chol, total cholesterol; T.P, total protein; WBC, white blood cells.

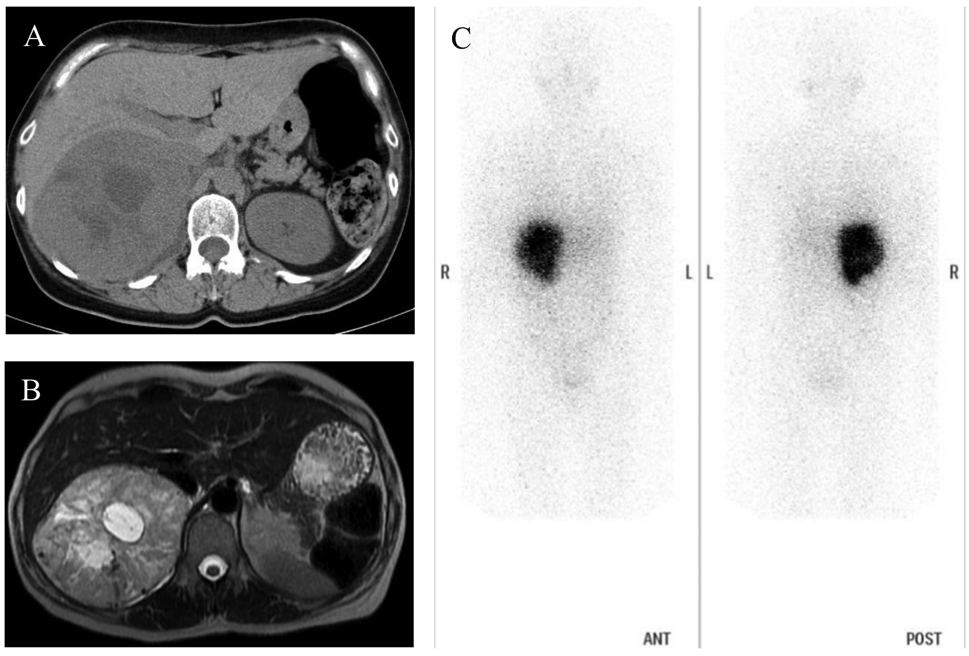

Figure 1. A, Computed tomography scans. B, magnetic resonance imaging. C, ^{123}I-metaiodobenzylguanidine scintigraphy of the right adrenal area.

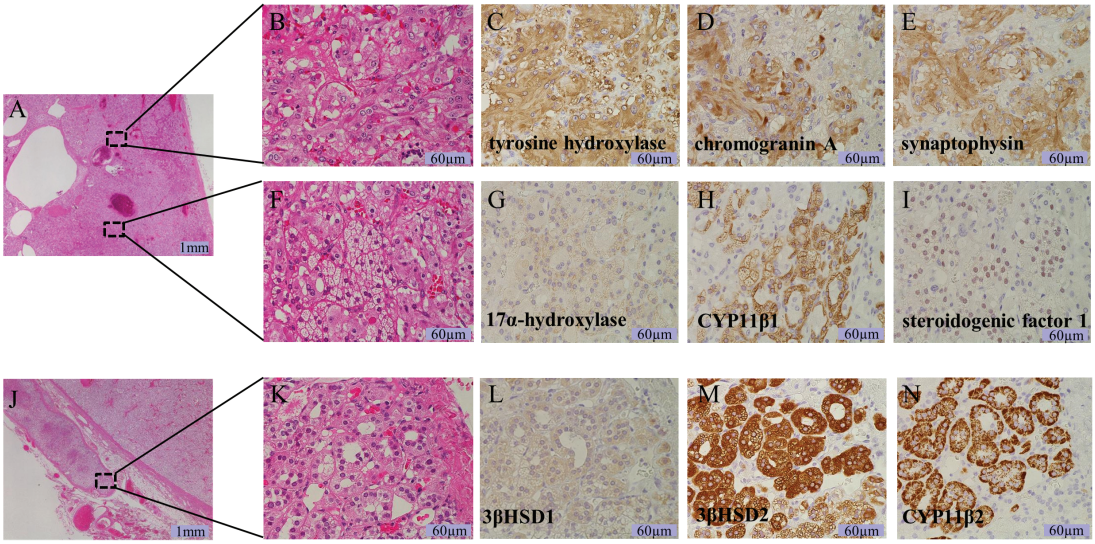

Figure 2. Hematoxylin and eosin staining, immunohistochemical staining of the resected adrenal gland. A, The tumor region at low magnification. The tumor consists of 2 components. The upper side shows the medullary component. The lower side shows the cortical components. The medullary component comprised approximately 90% of the lesion. B, At high magnification, the neoplastic cells had an alveolar and cord-like structure surrounded by small blood vessels. Immunohistochemical staining is positive for C, tyrosine hydroxylase; D, chromogranin A; and E, synaptophysin in the catecholamine-producing cells. F, At high magnification, a cluster of clear cells contains a bright, foamy cytoplasm and clear vacuolated cytoplasm with small dark nuclei. Immunohistochemical staining is positive for G, 17α-hydroxylase; H, 11β-hydroxylase (CYP11β1); and I, steroidogenic factor-1. J, Adrenal tissue adjacent to the encapsulated tumor at low magnification. Micronodules are observed in the zona glomerulosa. K, At high magnification, micronodules almost entirely consist of clear cells with abundant cytoplasm, which are not encapsulated. Immunohistochemical staining is L, negative for 3β-hydroxysteroid dehydrogenase1 (3βHSD1), and M, positive for 3β-hydroxysteroid dehydrogenase2 (3βHSD2) and N, 18-hydroxylase aldosterone synthase (CYP11β2) in the micronodules.

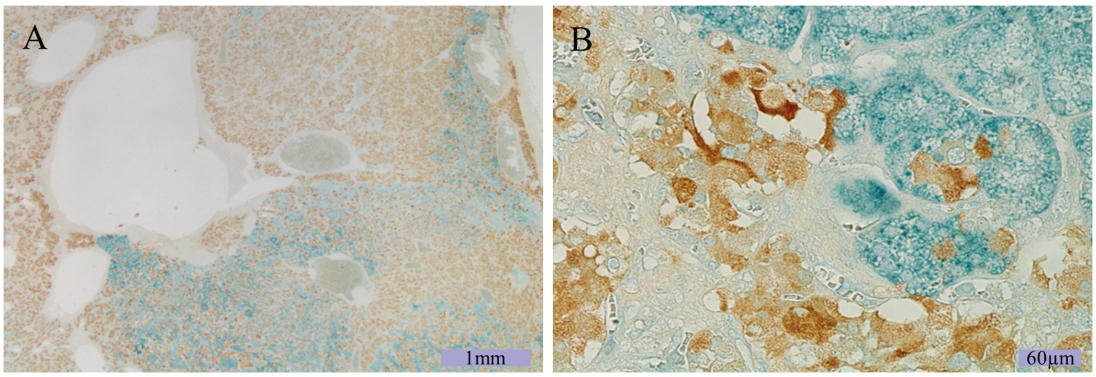

Figure 3. Double immunohistochemical staining for 11β-hydroxylase (CYP11β1) (blue chromogen) and chromogranin (brown chromogen). A, Low magnification B, High magnification.

18-hydroxylase aldosterone synthase (CYP11β2) (data not shown). Based on these histological findings and blood data, the tumor was diagnosed as an adrenocortical tumor harboring cortisol-producing ability. To further establish whether the 2 hormones, catecholamines and cortisol, were produced simultaneously in the same cell, double immunohistochemical staining was performed. No hybrid tumor cells producing both catecholamines and cortisol were detected in this lesion (Fig. 3). In addition, ectopic ACTH production by the pheochromocytoma has been reported to promote adrenal cortical tumor [9]; therefore, ACTH immunohistochemical staining was performed (Fig. 4). Cells positive for ACTH were detected within the lesion of pheochromocytoma cells.

An adjacent nonneoplastic adrenal gland was detected (Fig. 2J-2N). The zona fasciculata and reticularis of the adrenal cortex were histologically atrophied. Immunoreactivity of dehydroepiandrosterone-sulfotransferase in the zona reticularis, which reflects the long-term dynamics of the hypothalamus-pituitary-adrenal axis, was markedly suppressed. Therefore, cortisol produced by the tumor was considered to suppress the hypothalamus-pituitary-adrenal axis of this patient. In the zona glomerulosa of the nonneoplastic adrenal cortex, adrenocortical micronodular

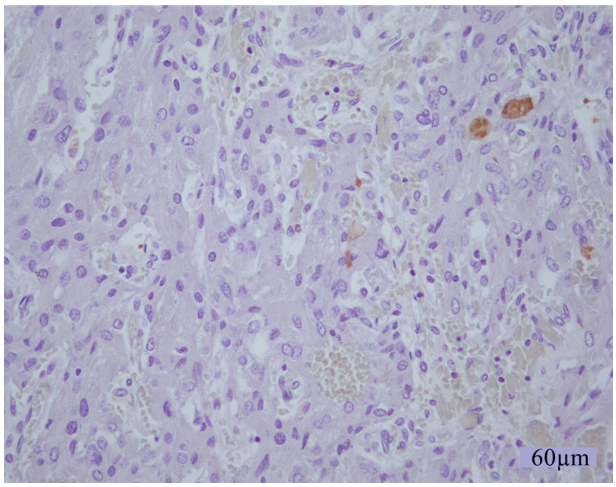

Figure 4. Immunohistochemical staining for adrenocorticotropin (ACTH).

lesions were detected, and further immunohistochemical analysis revealed the presence of unilateral adrenocortical micronodules rather than diffuse hyperplasia of the zona glomerulosa (Fig. 2L-2N).

The postoperative course of this patient was uneventful. Hydrocortisone replacement was performed until 6 months postoperatively. Both hypertension and diabetes mellitus clinically improved following the operation; her blood pressure was 119/70 mm Hg without antihypertensive agents, and her glycated hemoglobin A_{1c} level was 5.6% without antidiabetic drugs and insulin. Her endocrinology data were within the normal range, including noradrenalin (337 pg/mL [ref. 100-450 pg/mL]), ACTH (33.7 pg/mL [ref. 7.2-63.3 pg/mL]), cortisol (7.7 mg/dL [ref. 6.2-19.4 mg/dL]), and plasma aldosterone concentration (112 pg/mL [ref. 29.9-159 pg/mL]). Plasma renin activity was above the lower limit (0.3 ng/mL/h [ref. 0.3-2.9 ng/mL/h]), and aldosterone/renin ratio was elevated 373 (pg/mL)/(ng/mL/h) (ref. < 200 (pg/mL)/(ng/mL/h). The patient was well and had no signs of recurrence of the pheochromocytoma/adrenocortical tumor 9 years after the operation.

Discussion

We report a rare case of increased levels of 3 different adrenal hormones derived from the same adrenal gland. Two out of these 3 hormones, catecholamines and cortisol, were considered to be produced by MCMT, composed of 2 distinct cell populations without tumor cells positive for both medullary and cortical markers using immunohistochemistry. Regarding the third hormone, whether aldosterone production was autonomous could not be clinically determined before the adrenalectomy. If the patient had autonomous aldosterone production, adrenocortical aldosterone-producing micronodules in the zona glomerulosa of the adjacent nonneoplastic adrenal gland might be involved in the excessive aldosterone. Symptoms due to excess catecholamines secreted by the MCMT were present, but those due to the excess cortisol were not clinically evident, indicating that the patient presented with an ACTH-independent subclinical Cushing syndrome. However, it is unclear whether the aldosterone excess was functional or nonfunctional because it was masked by the presence of the pheochromocytoma.

The patient underwent surgical resection of the adrenal mass, which revealed the presence of MCMT consisting of 2 distinctively different populations of tumor cells, namely medullary and cortical cells. The adrenal medulla and cortex have separate and distinct embryological origins because they originate from different germ layers, the neuroectoderm, and the mesoderm, respectively. Therefore, the presence of 2 cell types of different origins in the same tumor is extremely rare. Whether the components of MCMTs (adrenocortical hyperplasia or adenoma, and pheochromocytoma) grow independently or are associated with each other have remained virtually unknown because of their rarity. Additionally, the etiology of MCMTs has remained unknown. However, several hypotheses have been proposed for the pathogenesis of this unique adrenal neoplasm [2, 5-9, 11, 14-18].

One hypothesis is that ectopic ACTH production by a preceding pheochromocytoma could account for the subsequent development of adrenocortical tumors. ACTH is known to be synthesized in the chromaffin cells of the adrenal medulla and is a major mediator of corticomedullary functional interaction in an autocrine and a paracrine manner [18]. Cushing syndrome due to ectopic ACTH production from adrenal medullary lesions is also extremely rare, and its cortisol hypersecretion generally occurs in an ACTH-dependent endocrine manner [14, 16, 17]. However, ACTH produced by a pheochromocytoma may also stimulate adjacent adrenocortical cells in a paracrine manner, leading to the development of adrenal tumors with hypercortisolism [18]. ACTH immunoreactivity identified in the pheochromocytoma and intermingled adrenocortical and pheochromocytoma tumor cells in the present case could therefore account for the development of the MCMT. However, further investigations are required for clarification.

Another hypothesis of the pathogenesis of this tumor is that the lesion may represent a collision tumor, which could have developed in a totally independent fashion. Namely, 2 adjacent tumors, 1 originating from the adrenal medulla and the other from the cortex, may have occurred simultaneously and subsequently combined. The boundary between the adrenocortical and medullary-derived cells was

not evident in this case, even after careful histopathological evaluation. However, the absence of hybrid tumor cells harboring the characteristics of medullary and cortical features could not rule out the possibility of collision tumors in this case.

Another hypothesis is that these 2 tumors of different origins may have been derived from a single stem cell [8]. This hypothesis has been reported to clearly explain the simultaneous occurrence of tumors derived from different germ layers in other organs [19]. Recently, a variant of fibroblast growth factor receptor-4 was reported to account for a case in which cells derived from medullary and cortical cells were identified in the same tumor cells [5]. However, in this case, the tumor did not contain any hybrid tumor cells, and it is improbable that this case could have been derived from a single stem cell. The last potential hypothesis of its pathogenesis is the disruption of intra-adrenal interaction between cortical and chromaffin cells. This interaction is required for normal adrenal gland function [2, 7]. Recently, adrenal corticomedullary interactions involving the influence of catecholamines on adrenal steroids were reported in patients with pheochromocytoma, but not paraganglioma [15]. The first increase in either cortisol or catecholamine stimulates the secretion of other hormones, resulting in a vicious cycle of proliferation [2, 6].

In this case, primary aldosteronism was not clinically suspected before surgery because the patient did not fulfill the diagnostic criteria of primary aldosteronism; namely, the aldosterone/renin ratio was less than 200 (pg/mL)/(ng/mL/h). Urinary aldosterone was excessive, but renin was not suppressed; therefore, autonomous aldosterone hypersecretion was not clinically suspected. In the presence of a pheochromocytoma, excess catecholamines could stimulate renin secretion, either through decreased renal perfusion pressure or the direct action of catecholamines on juxtaglomerular cells, resulting in the stimulation of aldosterone secretion. Hence, we could not rule out the possibility that hyperaldosteronism may have been masked in this case before adrenalectomy. In fact, under normal blood catecholamine conditions, the postoperative plasma renin activity was 0.3 ng/mL/h and the aldosterone/renin ratio was 373 (pg/mL)/(ng/mL/h). Together, these data suggest that the other adrenal gland of this patient might harbor adrenocortical lesions producing excessive aldosterone. However, saline suppression testing or captopril testing is needed to clarify this possibility. Eventually, it was difficult to determine whether aldosterone secretion from CYP11β2-positive adrenocortical micronodules in the resected adrenal gland was autonomous. This is because CYP11β2-positive adrenocortical micronodules are reportedly present in the adrenals from individuals without primary aldosteronism, and these micronodules have been postulated to be the origin or prodromal stage of primary aldosteronism [20]. MCMT accompanied by aldosterone-producing micronodules has not been reported in earlier studies, and only 9 cases of the combination of pheochromocytoma and primary aldosteronism have been reported in previous studies. In the case reported by Ohta et al [12], pheochromocytoma and aldosterone-producing adenoma were present separately in the adrenal gland. The simultaneous development of these 2 adrenal lesions involved in endocrine hypertension was therefore considered accidental, but it is also true that the functional correlation of these 2 lesions has remained controversial. Further studies on the possible association between MCMTs and aldosterone hypersecretion, or between pheochromocytoma and aldosterone hypersecretion, are warranted.

Conclusion

We report a case of an MCMT, consisting of cells of pheochromocytoma and adrenocortical cortisol-producing tumors. In addition, aldosterone-producing adrenocortical micronodules were detected in the zona glomerulosa of the nonneoplastic adrenal gland adjacent to the tumor. To the best of our knowledge, cases of the same adrenal gland causing elevated levels of 3 hormones (catecholamines, cortisol, and aldosterone) have not been reported in earlier studies. The analysis of this case confirmed the fact that a detailed histopathological analysis of complex adrenal tumors, such as in this case, could provide thought-provoking insights into the pathogenesis of adrenal tumors as well as the potential functional interplay of hormones in the adrenal gland.

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Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Additional Information

Correspondence: Hiroshi Ikegami, MD, PhD, Department of Endocrinology, Metabolism and Diabetes, Kindai University Faculty of Medicine, 377-2 Ohno-higashi, Osaka-sayama, Osaka 589-8511, Japan. Email: ikegami@med.kindai.ac.jp.

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Data Availability: Data sharing is not applicable to this article because no data sets were generated or analyzed during the present study.

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