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Abnormal glucose tolerance in a patient with pheochromocytoma and ACTH-independent subclinical Cushing's syndrome involving the same adrenal gland

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Abstract

Coexistence of adrenocorticotropin hormone (ACTH)-independent subclinical Cushing's syndrome (SCS) with pheochromocytoma involving the same adrenal tumor is rare. Moreover, no previous reports have compared pre- and postoperative insulin sensitivities in these cases. A 74-year-old woman was admitted to our hospital with hyperhidrosis, dry mouth, and weight loss. Pheochromocytoma was suspected based on elevated circulating catecholamines, and was confirmed by scintigraphy and histopathological analysis. Laboratory data, low ACTH, and lack of a diurnal cortisol rhythm indicated coexisting Cushing's syndrome (CS). The atypical symptoms of CS and lack of cortisol suppression after 1 and 8 mg dexamethasone suppression tests confirmed the diagnosis of SCS. Histopathological analysis demonstrated autonomous cortisol production caused by paracrine stimulation from the pheochromocytoma. Her fasting plasma glucose level on admission was 372 mg/dL and her hemoglobin (Hb) A1c was 11.0%. HbA1c decreased to

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5.2% postoperatively, with improved insulin secretion indicated by homeostasis model assessment β (18.1 to 45) and urinary C-peptide (26.5 to 48.5 mg/day). Herein we report a rare case of pheochromocytoma and SCS involving the same adrenal tumor, with the first documented levels of glucose tolerance before and after surgery. Coexisting SCS should thus be considered in patients with pheochromocytoma presenting with severely uncontrolled diabetes mellitus.

Keywords
Diabetes, subclinical Cushing's syndrome, pheochromocytoma, adrenocorticotropin hormone, glucose tolerance, adrenal gland

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Introduction

Subclinical Cushing's syndrome (SCS) is characterized by endogenous hypercortisolism without the typical symptoms of overt Cushing's syndrome (CS). However, criteria for diagnosing SCS have not yet been established, and the prevalence of SCS among adrenal incidentalomas has thus reportedly varied from 6% to 15%.[1–3] Patients with SCS exhibit a lack of dexamethasone suppression, increased urinary free cortisol excretion, blunted circadian cortisol rhythms, low adrenocorticotropic hormone (ACTH) levels, blunted ACTH responses to corticotropin-releasing hormone, and reduced dehydroepiandrosterone sulfate (DHEAS) levels. In addition, pheochromocytoma is a very rare disease with an incidence of 1 to 10 cases per million people.[4–6] The coexistence of hypercortisolism with tumors of the adrenal medulla secreting high levels of catecholamines has been reported previously. Most cases of pheochromocytoma associated with SCS or CS are caused by ACTH or ACTH precursors produced by the pheochromocytoma, with resulting bilateral adrenocortical hyperplasia.[7,8] However, few studies have documented the combination of ACTH-independent SCS and pheochromocytoma involving the same adrenal gland.[1,9,10]

Darko et al.[11] reported the first case of severe postoperative hypoglycemia in a patient with pheochromocytoma and SCS and emphasized the importance of monitoring blood glucose levels postoperatively. Very few cases to date have described pheochromocytoma and SCS in the same adrenal gland, and none have also reported on the pre- and postoperative changes in glucose tolerance, especially insulin secretory capacity. Herein, we report a very rare case of a patient with both ACTH-independent SCS and pheochromocytoma involving the same adrenal gland, with assessments of glucose tolerance throughout their clinical course.

Case report

A 74-year-old Japanese woman presented to a local clinic with symptoms of hyperhidrosis, dry mouth, weight loss, and fatigue. She had no past or family history of diabetes. She had been aware of a tremor for 2 years and had suffered from hyperhidrosis, dry mouth, fatigue, and polyuria for the previous 2 months. Hypertension (176/100 mmHg) and a 4 kg weight loss in 3 months (from 67 to 63 kg) were noted. Initial laboratory tests revealed overt diabetes (fasting plasma glucose (FPG) concentration 372 mg/dL and hemoglobin (Hb) A1c

11.0%) and all three blood catecholamine fraction values were high (adrenaline 611 pg/mL, noradrenaline 1666 pg/mL, dopamine 31 pg/mL). After starting oral nifedipine CR 40 mg and glimepiride 2 mg at a local clinic, she was referred to our hospital for further investigation and treatment.

On admission to our hospital, her weight was 63.2 kg, height 159.1 cm, body mass index 25.0 kg/m^2, blood pressure 169/98 mmHg, and heart rate 82/minute with a regular rhythm. There were no clinical signs of cortisol excess. Laboratory data revealed no significant positive findings. The hormone analysis results are summarized in Figure 1 and Table 1. Plasma and urinary metanephrine and normetanephrine, as well as urinary adrenaline and noradrenaline, were more than three times the upper limits of their normal ranges. Her 24-hour urinary free cortisol and basal serum cortisol levels were normal but no diurnal rhythms were observed and her ACTH level was relatively low. The results of 1 mg and 8 mg dexamethasone suppression tests (DST) demonstrated a lack of serum cortisol suppression. The lack of dexamethasone suppression in combination with low ACTH and high catecholamine levels strongly suggested the coexistence of pheochromocytoma with a cortisol-producing adrenal tumor. Abdominal computed tomography (CT) revealed a 4 cm well-encapsulated left adrenal tumor, while the right adrenal gland was normal (Figure 2a and b). Magnetic resonance imaging of the sella turcica showed no abnormalities. We performed ^{131}meta-iodobenzyguanidine (MIBG) scintigraphy, which demonstrated high accumulation in the upper left abdomen (Figure 2c). On the basis of these findings, concurrent pheochromocytoma and SCS were diagnosed. Preoperative examination revealed no evidence of multiple endocrine neoplasia 2a. Diabetes was also diagnosed with coexisting low insulin secretory capacity (Figure 3 and Table 2). After completion of the examination, her blood

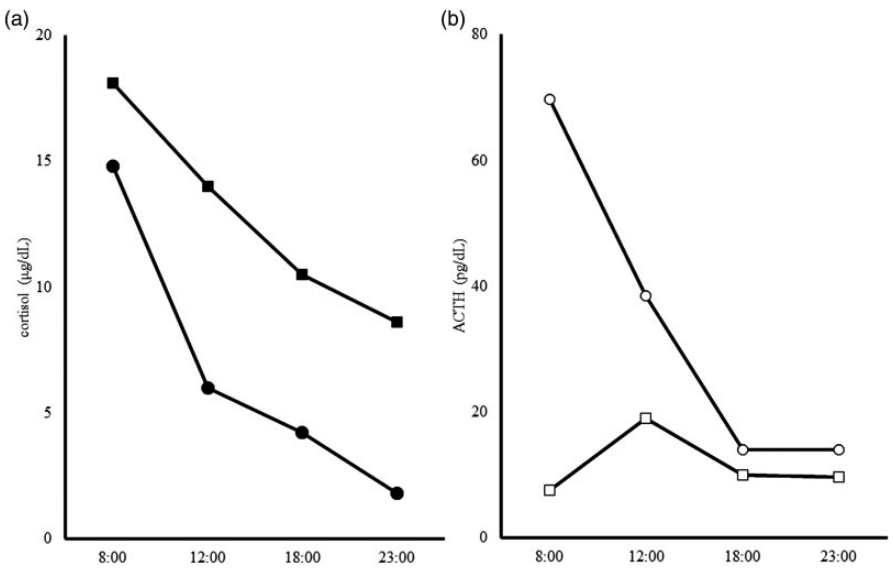

Figure 1. Change in circadian cortisol and ACTH rhythm before and after surgery. (a) Circadian cortisol rhythm; (b) circadian ACTH rhythm. Cortisol before surgery (■), cortisol after surgery (●), ACTH before surgery (□), ACTH after surgery. ACTH: adrenocorticotropin hormone.

Table 1. Endocrine analysis results at presentation and after surgery.

	Preoperative	Postoperative	Normal range
Plasma			
Basal cortisol (μg/dL)	18.1	14.8	
1 mg DST (μg/dL)	14.3	0.4	<1.8
8 mg DST (μg/dL)	11.7	0.5	<1
Adrenaline (pg/mL)	904	7	≤100
Noradrenaline (pg/mL)	2046	162	100–450
Dopamine (pg/mL)	31	≤5	≤20
Urine			
UFC (μg/day)	78.0	38.8	11.2–80.3
Adrenaline (μg/day)	390.4		2–31
Noradrenaline (μg/day)	646.7		29–151
VMA (mg/day)	14.5		1.5–4.3
Metanephrine (mg/day)	5.28		0.04–0.18
Normetanephrine (mg/day)	2.11		0.1–0.28

DST: dexamethasone suppression test, UFC: urinary free cortisol, VMA: vanillylmandelic acid.

pressure was controlled with 4 mg of doxazosin, and her mean blood pressure then dropped to $135 \pm 5/80 \pm 10$ mmHg. Glucose control was achieved with basal insulin injection (16 U insulin glargine) and 50 mg of sitagliptin. After stabilization of her condition, the patient underwent laparoscopic left adrenalectomy. Hydrocortisone 50 mg/day had been started preoperatively at the diagnosis of SCS, and this was then tapered over the next 20 days. Insulin and oral hypoglycemic agents were discontinued immediately after surgery and her blood glucose level stabilized at 80–120 mg/dL. Doxazosin mesilate was switched to 2.5 mg amlodipine and tapered, with the same timing as the hydrocortisone. No symptoms of adrenal insufficiency, such as hypotensive episodes and hypoglycemia, were observed during or after surgery, and her basal cortisol was 11.7 μg/dL after discontinuation of hydrocortisone. The resected mass measured approximately $75 \times 47 \times 41$ mm, weighed 40 g, and was well-encapsulated. The cut surface of the resected tumor was reddish and solid with petechial hemorrhages (Figure 4a and b). Pathological findings were consistent with a pheochromocytoma, including immunohistochemical positivity for both chromogranin A (Figure 5a) and synaptophysin staining (Figure 5b), as well as the presence of a few MIB-1-positive cells stained with Ki-67 antibody. ACTH immunostaining was weakly positive in only a few areas of the pheochromocytoma, and ACTH-positive cells in the cytoplasm were considered to be part of the zona reticularis based on its morphology (Figure 5c). There was no immunostaining for SF-1, a characteristic of adrenal cortex marker, within the pheochromocytoma (Figure 5d). The adrenal cortex appeared histologically normal and no cortical adenomatous tissue or adrenocortical hyperplasia was observed. However, DHEA sulfotransferase (DHEAST) expression was elevated in areas of the adrenal cortex adjacent to the pheochromocytoma, and both CYP17A1 and CYP11B1 were also present (Figure 6).

The patient was hospitalized 4 months after the operation for glucose tolerance examinations and hormone analysis. Her FPG level and HbA1c had improved remarkably to 91 mg/dL and 5.2%, respectively. Moreover, her insulin secretory capacity had recovered and her insulin

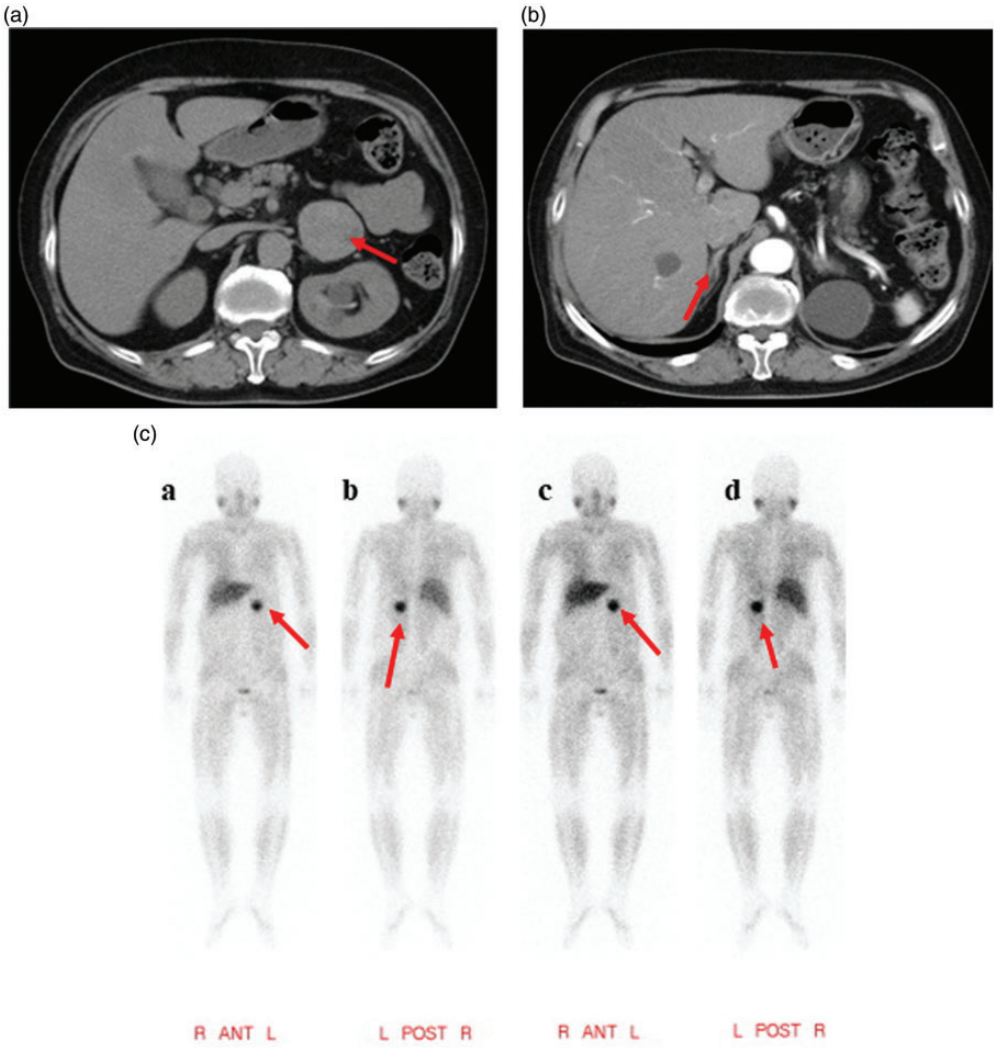

Figure 2. Computed tomography (CT) and ^{131}meta-iodobenzyguanidine (MIBG) scintigraphy. (a, b) Abdominal CT showing 4 cm well-encapsulated left adrenal tumor (red arrow) (a) with a clearly normal right adrenal gland (red arrow) (b). (c) ^{123}I-MIBG scintigraphy at (i, ii) 4 and (iii, iv) 24 hours. ^{123}I-MIBG scintigraphy showing high accumulation in the adrenal tumor located on the left side of the abdomen.

resistance showed a trend towards improvement (Table 2). The patient underwent a 75 g oral glucose tolerance test, which showed blood glucose levels of 88, 137, 200, 219, and 232 mg/dL and plasma insulin levels of 2, 10, 22, 26 and 42 U/mL at 0, 30, 60, 90, and 120 minutes, respectively. The insulinogenic index was 0.16, suggesting that glucose-induced first-phase insulin secretion was delayed, and the patient thus required long-term follow-up focused on her glucose tolerance. However, her circadian cortisol rhythm and ACTH level showed normalization (Figure 1).

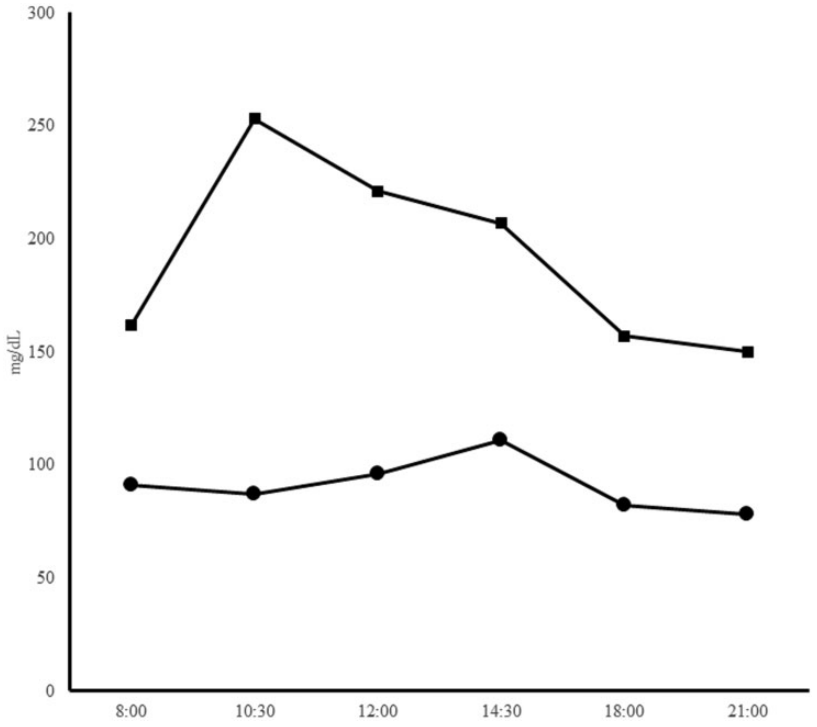

Figure 3. Blood glucose levels before and after a meal. (Meals eaten at 8 am, 12 noon and 6 pm). Changes in serum glucose concentrations before (■) and after surgery (●).

Written informed consent was obtained from the patient for publication of this report.

Discussion

The present patient had a left adrenal gland tumor identified during investigations related to her symptoms of hyperhidrosis, dry mouth, and fatigue. It was a relatively typical pheochromocytoma with overt diabetes, based on blood and urinary data, CT, and MIBG scintigraphy findings. However, autonomic cortisol secretion performed to exclude a cortical adenoma raised the suspicion of a coexisting SCS. SCS is diagnosed by biochemical evaluations to assess the hypothalamic pituitary-adrenal axis, based on measurements such as DST, 24-hour urinary free cortisol, morning plasma ACTH levels, cortisol rhythm, midnight serum cortisol levels and ACTH, as well as the cortisol response to corticotropin-releasing hormone stimulation. According to the diagnostic criteria, the current patient was diagnosed with SCS based on a blunted diurnal cortisol rhythm and failure of cortisol suppression on a 1 mg DST.[12–14] We were unable to examine the uptake of ^{131}I-adosterol scintigraphy to determine if the pheochromocytoma and SCS coexisted in the same adrenal gland; however, the circadian cortisol rhythm and the suppression on both 1 and 8 mg DST tests normalized after adrenalectomy. Furthermore, the initially low ACTH value increased remarkably after adrenalectomy, further supporting the coexistence of SCS in the same adrenal gland as the pheochromocytoma.

Table 2. Glucose tolerance test results before and after surgery.

	Preoperative	Postoperative
HbA1c (%)	11.2	5.2
Treatment	1400 kcal (24.9 kcal/kg) Glimepiride 2 mg	1400 kcal (24.9 kcal/kg) None
CPR (ng/mL) 8:00/10:30	1.81/1.57	1.01/2.81
IRI (μU/mL) 8:00/10:30	5/<1	3/7
HOMA-R	2	0.6
HOMA-β	18.1	45
Urine CPR (μg/day) (normal range 40–100)	26.5	48.5

CPR: C-peptide, IRI: immunoreactive insulin, HOMA-R: homeostasis model assessment ratio, HOMA-β: homeostasis model assessment beta cell.

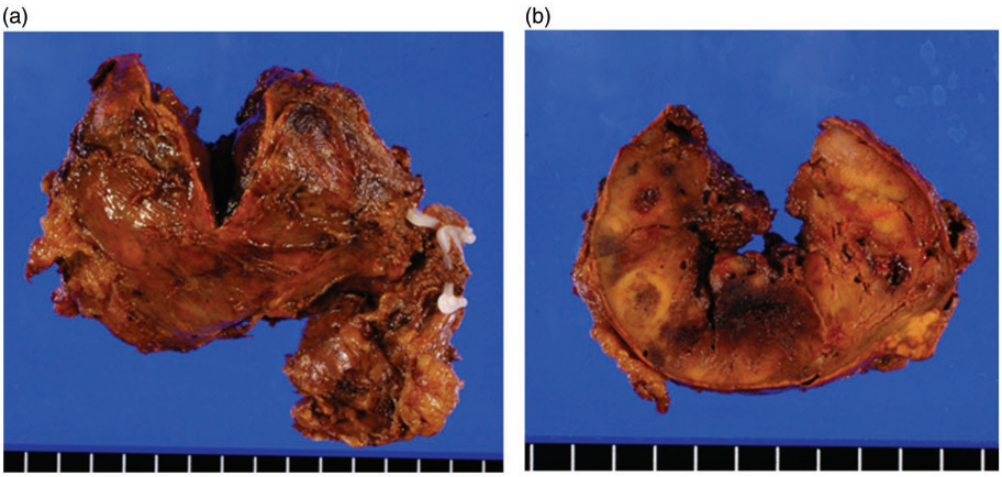

Figure 4. Macroscopic findings of the resected mass. (a) Mass before division was 75 × 47 × 41 mm and weighed 40 g; (b) mass after division showed reddish divided surface with petechial hemorrhages.

Negative staining for SF-1, as a marker of steroid-producing cells, demonstrated that the pheochromocytoma tumor cells did not have adrenal cortex characteristics, thus ruling out a collision and a composite tumor. The fact that the circulating ACTH levels were initially suppressed but became remarkably elevated after adrenalectomy, together with the absence of bilateral adrenal hyperplasia on CT scan, also denied the possibility of ectopic ACTH production by the pheochromocytoma resulting in autonomous cortisol secretion, even though ACTH immunostaining was slightly positive. DHEAST expression was elevated compared with the normal adrenal cortex, and both CYP17A1 and CYP11B1 were expressed in the adrenal cortex adjacent to the pheochromocytoma. These observations suggested that the cortisol was derived

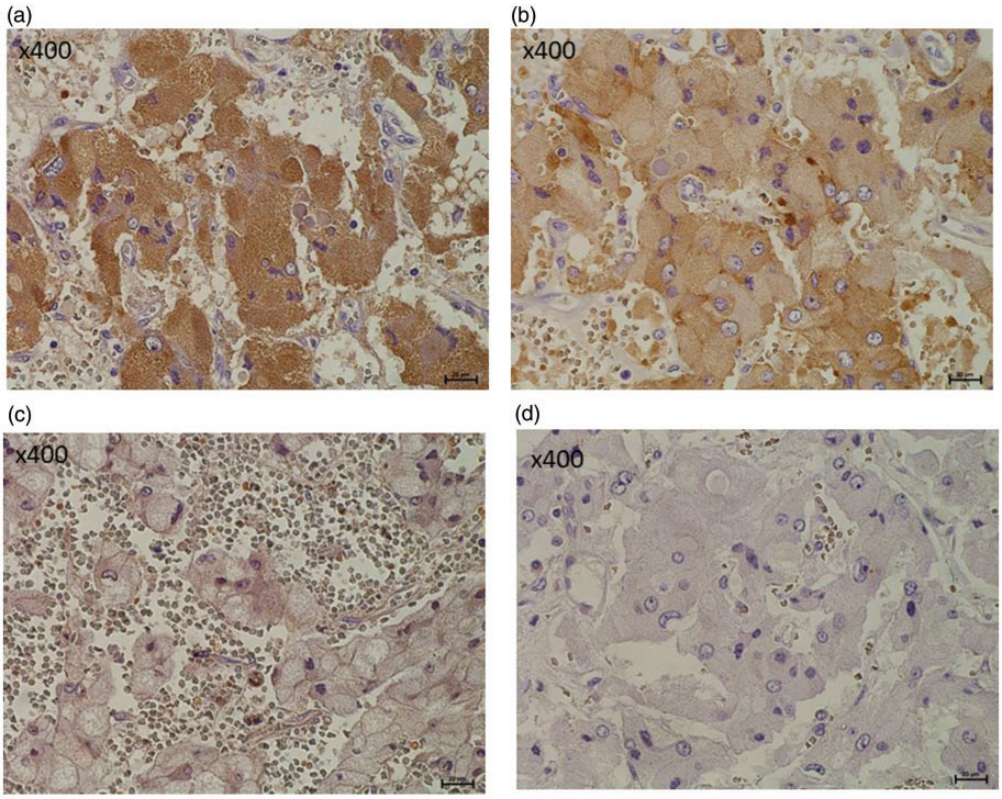

Figure 5. Immunohistochemical results. (a) Chromogranin A-positive, (b) synaptophysin-positive, (c) ACTH staining slightly positive in some areas, and (d) SF-1-negative within the pheochromocytoma.

from the adrenal cortex adjacent to the pheochromocytoma. Taken together, these findings suggest a possible mechanism involving autonomous cortisol secretion from the adjacent adrenal cortex, reflecting the paracrine actions of the pheochromocytoma and other factors.

Catecholamines and cortisol are known to modulate glucose homeostasis. Catecholamines inhibit insulin secretion via the $\alpha 2$ receptor,[15] and this decreased insulin secretion is considered to be the main reason for the characteristic glucose metabolism disorder in pheochromocytoma. In contrast, cortisol excess causes insulin resistance.[16] However, the mechanism by which the combination of catecholamines and cortisol impact on glucose homeostasis remains unclear. Sixteen previous cases of pheochromocytoma and ACTH-independent CS originating from the same adrenal gland have been reported,[1,9–11] including eight with overt diabetes; however, pre- and postoperative glucose tolerances have only been reported in two cases. Finkenstedt et al.[10] reported an ACTH-independent SCS and pheochromocytoma in a pregnant woman, with HbA1c 9.1% and FPG 218 mg/dL at her first visit, which improved to 6.4% after surgical tumor removal. Yaylali et al.[1] were the first to report the insulin sensitivity

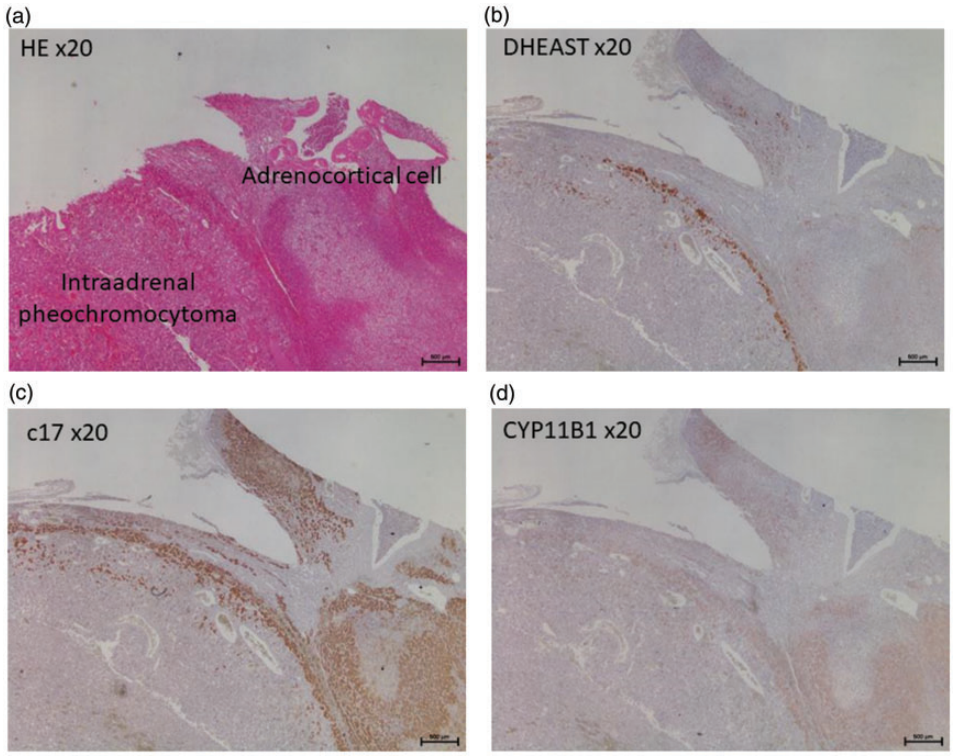

Figure 6. Immunohistochemical results. (a) Hematoxylin and eosin ×20; (b) DHEAST expression was enhanced in the adrenal cortex adjacent to the pheochromocytoma; (c) CYP17A1 (d) and CYP11B1 detectable in the adrenal cortex adjacent to the pheochromocytoma. HE: hematoxylin and eosin, DHEAST: dehydroepiandrosterone sulfotransferase.

in an incidentally discovered pheochromocytoma combined with ACTH-independent SCS. The patient's HbA1c was 14.3% with metformin 1700 mg/day. Their FPG, serum C-peptide level, and fasting insulin were 335 mg/dL, 1.77 ng/mL, and 26.5 IU/mL, respectively, indicating the existence of insulin resistance. In this case, more than 150 U of insulin per day were required to control the patient's blood sugar concentration. Her HbA1c decreased dramatically to 6.2% postoperatively, and her FPG fell to 116 mg/dL with only metformin 2000 mg/day. However, information on her postoperative insulin sensitivity was lacking. In the current case, the patient's insulin secretory capacity recovered after surgery (i.e. HOMA-β 18.1 to 45, urinary C-peptide 26.5 to 48.5 mg/day), resulting in a remarkable decrease in HbA1c from 11.2% to 5.2% without medication. Decreased insulin secretion was therefore considered to be the main pathology responsible for aggravating the glucose metabolism disorder. However, we did not perform a hyperinsulinemic-euglycemic clamp and the coexistence of insulin resistance could therefore not be determined.

Otsuki et al.[17] reported that FPG was lower in patients with CS compared with controls without CS, even though their HbA1c levels were the same. Similarly, Mazziotti et al.[18,19] reported that more than 50% of diabetic patients with CS had

a normal FPG, and emphasized the importance of measuring HbA1c or performing an oral glucose tolerance test. It might be speculated that hyperinsulinemia due to CS prevents hepatic glucose production in the fasting state. On the other hand, many studies have reported high FPG in patients with pheochromocytoma.[20,21] However, most cases were borderline diabetes, including one study that analyzed various parameters related to insulin secretion or insulin sensitivity in 11 patients with pheochromocytoma, with a mean HbA1c of $5.92 \pm 0.73\%$,[22] and only few cases required insulin treatment.[23,24] This may be explained by high levels of catecholamines preventing basal insulin secretion via the $\alpha 2$ receptor. A review of past cases suggests that patients with pheochromocytoma combined with ACTH-independent SCS have higher FPG levels than patients with pheochromocytoma alone,[1,10] similar to the current case. This might be attributed to the combined effects of catecholamine and cortisol. Cortisol increases postprandial glucose levels, and the elevated glucose is not normalized because of decreased basal insulin secretion due to catecholamine. The current report provides the first evidence to support this hypothesis by presenting the recovery of HOMA-β and reduced fasting immunoreactive insulin after tumor resection (Table 2). However, further evaluation of similar clinical cases is necessary to understand this relation.

Coexisting SCS and pheochromocytoma derived from the same adrenal gland has rarely been reported, but it is necessary to consider endogenous hypercortisolism diseases, such as SCS, and to follow-up affected patients to avoid adrenal insufficiency following surgery for any adrenal mass. To the best of our knowledge, no prior case reports have documented glucose tolerance throughout the patient's clinical course, allowing comparison of pre- and postoperative values. Herein, we present a patient with ACTH-independent SCS and pheochromocytoma involving the same adrenal gland, who demonstrated significant improvements in glucose tolerance and insulin secretion after adrenalectomy. Coexisting SCS should be considered in patients with pheochromocytoma presenting with severely uncontrolled diabetes mellitus.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest, besides N.M being an employee of AstraZeneca.

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