INTERNAL MEDICINE

□ CASE REPORT □

Somatostatin-secreting Pheochromocytoma Mimicking Insulin-dependent Diabetes Mellitus

Hiroyuki Hirai[1], Sanae Midorikawa[1,2], Shinichi Suzuki[3], Hironobu Sasano[4], Tsuyoshi Watanabe[1] and Hiroaki Satoh[1]

Abstract

We herein present the findings of a 42-year-old woman with either adrenal pheochromocytoma or intraadrenal paraganglioma that simultaneously secreted somatostatin, thus mimicking insulin-dependent diabetes mellitus. Pheochromocytoma was clinically diagnosed based on scintigraphy, elevated catecholamine levels, and finally a histopathological analysis of resected specimens. The patient had diabetic ketosis, requiring 40 U insulin for treatment. Following laparoscopic adrenalectomy, insulin therapy was discontinued and the urinary c-peptide levels changed from 5.5-9.0 to 81.3-87.0 μg/day. Histologically, somatostatin immunoreactivity was detected and the somatostatin levels were elevated in the serum-like fluid obtained from the tumor. Clinicians should be aware of the possible occurrence of simultaneous ectopic hormone secretion in patients with pheochromocytoma.

Key words: pheochromocytoma, secondary diabetes, urine c-peptide, catecholamine, somatostatin

(Intern Med 55: 2985-2991, 2016)
(DOI: 10.2169/internalmedicine.55.7071)

Introduction

Pheochromocytoma or intraadrenal paraganglioma, an endocrine disease of the adrenal medulla, is well known to secrete large amounts of catecholamines, which can induce clinical glucose metabolism abnormalities in approximately 25-75% cases (1). In patients with pheochromocytoma, both the amounts and types of catecholamine vary enormously among individual patients, thereby resulting in a wide range of reported incidences of diabetes mellitus (2). Furthermore, pheochromocytoma occasionally simultaneously secretes various hormones (3). At this juncture, the main mechanism of glucose metabolism disorder in pheochromocytoma is considered to be due to both insulin secretion and resistance (2), but its exact pathogenesis has not yet been completely elucidated.

Somatostatin was first isolated from the hypothalamus of a mammal in 1973 and was initially recognized as a potent inhibitor of the growth hormone secretion (4), but at this juncture, somatostatin is considered to be a universal inhibitor of peptide secretion which inhibits various hormone secretions, including insulin (5). There have been, however, only a few reports on simultaneous somatostatin-catecholamine secreting pheochromocytomas (3, 6). In this study, we report a case of pheochromocytoma clinically mimicking insulin-dependent diabetes mellitus due to ectopic somatostatin-secretion.

Case Report

In June 2004, a 42-year-old woman presented to the hospital with intermittent complaints of thirst, nausea, dizziness, and peripheral numbness lasting for approximately 1 month. During 6 months prior to her hospital visit, she had lost approximately 14 kg of body weight (from 62 to 48 kg). She had no contributory past history but a positive family history of diabetes in her maternal grandfather. Laboratory examination revealed a high plasma glucose level (518 mg/dL) and ketonuria was positive and a clinical diagnosis of diabetic

[1]Department of Nephrology, Hypertension, Diabetology, Endocrinology, and Metabolism, Fukushima Medical University, Japan, [2]Department of Radiation Health Management, Fukushima Medical University, Japan, [3]Department of Thyroid and Endocrinology, Fukushima Medical University, School of Medicine, Japan and [4]Department of Pathology, Tohoku University, Graduate School of Medicine, Japan
Received for publication January 5, 2016; Accepted for publication March 7, 2016
Correspondence to Dr. Hiroaki Satoh, hiroakis-tky@umin.ac.jp

Table 1. Laboratory Data on Admission.

Parameter	Result	Unit	Parameter	Result	Unit
WBC	5,600 (2,800–8,800)	/μL	Na	139 (138–146)	mEq/L
RBC	416 (366–478) × 10^4	/μL	K	4.8 (3.6–4.9)	mEq/L
Hb	13.2 (11.6–14.0)	g/dL	Cl	104 (99–109)	mEq/L
Hct	39.7 (34.1–41.7)	%	BUN	10.0 (8.0–22.0)	mg/dL
Plt	36.1 (14.7–34.1) × 10^4	/μL	Cre	0.60(0.40–0.70)	mg/dL
			UA	6.0 (2.3–7.0)	mg/dL
TP	6.5 (6.7–8.3)	g/dL	CK	40 (45–163)	IU/L
Alb	3.8 (3.9–4.9)	g/dL	TC	340 (150–219)	mg/dL
AST	17 (13–33)	IU/L	TG	102 (30–150)	mg/dL
ALT	18 (6–27)	IU/L	HDL-C	60 (49–74)	mg/dL
LDH	197 (119–229)	IU/L	CRP	0.30 (<0.30)	mg/dL
AlP	113 (115–359)	IU/L			
γ-GTP	32 (10–47)	IU/L	FPG	196 (70–109)	mg/dL
Ch-E	293 (214–466)	IU/L	HbA1c	13.0 (4.7–6.2)	%
T-Bil	0.8 (0.2–1.2)	mg/dL			
TSH	0.665 (0.500–5.00)	μIU/mL			
FT4	0.97 (0.90–1.70)	ng/dL		Urine test	
ACTH	7.08 (7.20–63.3)	pg/mL	U-Glucose	(4+)	
Cortisol	9.48 (6.20–19.4)	μg/dL	U-Protein	(–)	
DHEA-S	518 (210–2,120)	ng/ml	U-Ketone	(±)	
PRA	2.18 (0.30–2.90)	ng/mL/hr	U-Blood	(–)	
ALD	142 (29.9–159)	pg/mL			
CEA	4.4 (<4.9)	ng/mL			
Calcitonin	14.0 (<6.2)	pg/mL			

ACTH: adrenocorticotropic hormone, Alb: albumin, ALD: Aldosterone, AlP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, CEA: carcinoembryonic antigen, Ch-E: Cholinesterase, CK: creatine, Cl: chloride, Cre: creatinine, CRP: C reactive protein, DHEA-S : dehydroepiandrosterone sulfate, FPG: fasting plasma glucose, FT4: free thyroxine, γ-GTP: γ-glutamyl transpeptidase, Hb: hemoglobin, Hct: hematocrit, HDL-C: high density lipoprotein cholesterol, K: potassium, LDH: lactic dehydrogenase, Na: sodium, Plt: platelets, PRA : plasma renin activity, RBC: red blood cells, T-Bil: total bilirubin, TC: total cholesterol, TG: triglyceride, TP: total protein, TSH: thyroid stimulating hormone, UA: uric acid, WBC: white blood cells

ketosis was made. Continuous saline and insulin were intravenously administered and the form of insulin administration was changed from an intravenous to a subcutaneous injection [human regular insulin (Humulin R) and neutral protamine Hagedorn (Humulin N)], and the dose was gradually increased. At 3 weeks after hospitalization, the preprandial blood glucose level was approximately 150 mg/dL following Humulin R (10-10-10 U) and Humulin N (0-0-0-10 U) administration. Abdominal ultrasound revealed a massive right adrenal tumor measuring approximately 5 cm in diameter. The patient was subsequently referred to our hospital for further examination and treatment.

On admission to our hospital, physical examination revealed no significant positive findings, i.e., height, 156.9 cm; body weight, 49.5 kg; body mass index, 20.5 kg/m^2; body temperature, 36.6°C; blood pressure, 120/82 mmHg; and pulse, 84/min, regular rhythm. Her thyroid was slightly enlarged on palpation but abdomen was unremarkable. The laboratory data on admission are summarized in Table 1. Her fasting plasma glucose level was 196 mg/dL and HbA1c level was 13.0%. Computed tomography of the abdomen was performed and revealed a huge right adrenal mass (Fig. 1A) with a heterogeneous internal structure. Iodine-131-meta -iodobenzylguanidine (MIBG) scintigraphy then demonstrated an accumulation in this right adrenal tumor (Fig. 1B). As shown in Table 2, a high catecholamine level was detected in the urine, and in particular, both noradrenaline and adrenaline levels were markedly elevated. Therefore, we diagnosed the tumor to be pheochromocytoma. Although a slight diffuse thyroid enlargement and slightly elevated serum calcitonin levels were detected, thyroid ultrasound revealed only a small cyst, with no evidence of any tumor, including medullary carcinoma of the thyroid. Considering her history and the result of examinations, we ruled out multiple endocrine neoplasia. We did not perform the clonidine suppression test in this patient because her urinary catecolamine levels were extremely high, as in essential hypertension; also, because her blood pressure was almost normal, there was a risk of inducing hypotension with the clonidine suppression test.

On day 7 after admission, her energy intake was 1,600 kcal, and despite Humulin R (10-8-10 U) and Humulin N (0-0-0-12 U) administrations, her blood glucose profile was 231, 242, 243, 177, 178, 119, and 175 mg/dL at 7:30, 10:00, 11:30, 14:00, 17:30, 20:00, and 23:00, respectively. In addition, her urinary c-peptide level was low at 5.5-9.0 μg/day. (normal range: 40.0-100.0 μg/day) (Table 2). Therefore, she was suspected to have insulin-dependent diabetes mellitus. Further testing failed to detect either glutamic acid decarboxylase antibodies or islet cell antibodies. Her plasma glucose level gradually improved following basal-bolus insulin therapy. In parallel, doxazosin was administered at a

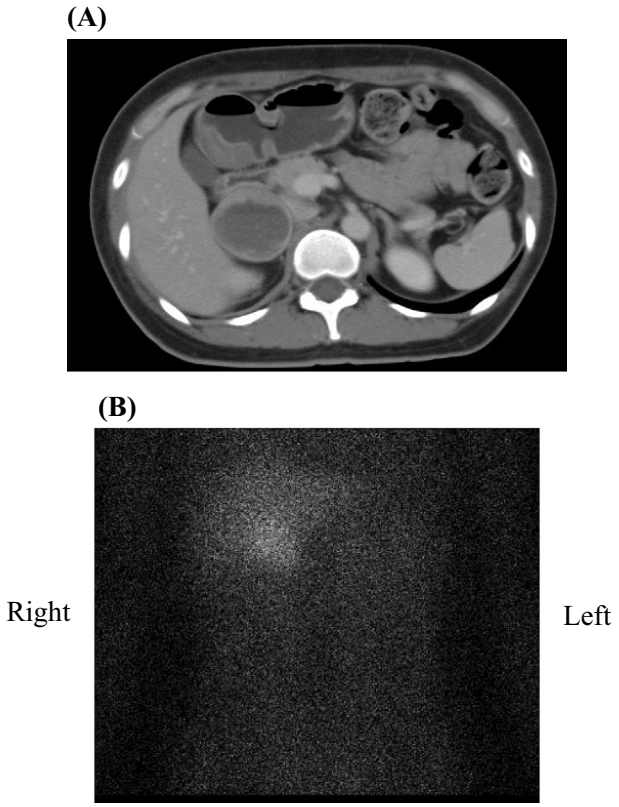

Figure 1. Computed tomography and iodine-131-meta-iodobenzylguanidine (MIBG) scintigraphy. (A) Abdominal computed tomography showing a huge right adrenal tumor, covered by a film, and with a heterogeneous internal structure. (B) MIBG scintigraphy showing an area of accumulation in the right adrenal tumor.

dose of 1 mg on day 10, and the dose was gradually increased. Furthermore, carvedilol was additionally administered at a dose of 10 mg on day 25, and the dose was thereafter gradually increased. Her blood pressure level was approximately 100-120/60-80 mmHg. Approximately 1 week before surgery, her energy intake was 1,600 kcal, and her blood glucose profile was 171, 169, 149, 144, 139, 131, and 99 mg/dL at 7:30, 10:00, 11:30, 14:00, 17:30, 20:00, and 23:00, respectively, following Humulin R (10-6-8 U) and Humulin N (0-0-0-12 U) administrations. In addition, before surgery, the dose concentrations of doxazosin and carvedilol were 4 mg and 20 mg, respectively. A fundus examination of the eye did not reveal any diabetic changes but slight hypertensive changes were observed, despite a negative history of hypertension.

On day 38 after admission, laparoscopic adrenalectomy was performed and the right adrenal tumor was removed without any complications. The resected mass was well encapsulated and measured 5.0×5.0×5.5 cm in size (Fig. 2). The surface of the tumor appeared brownish and the cut surface a tan to light gray hue with irregular cystic structures containing serous fluid. No foci of hemorrhage or necrosis were identified in the tumor. Representative histopathological findings are summarized in Fig. 3A. A histological examination revealed proliferative tumor cells with an alveolar pattern or the-so-called "zell-ballen" pattern, mimicking adrenal medullary cells. Somatostatin, chromogranin, synaptophysin, and neuron specific γ-enolase were all immunohistochemically positive in tumor cells but neurofilament negative (Fig. 3B; data only shown for somatostatin). The somatostatin level in the serum-like intratumoral fluid was 98 pg/mL (normal range in peripheral blood: 1.0-12 pg/mL). This tumor was subsequently diagnosed as being either pheochromocytoma or intraadrenal paraganglioma associated with ectopic somatostatin production and secretion.

Despite postoperative hypoglycemia requiring, 4.3-10% glucose or 40-220 g/day of glucose for 5 days, hypoglycemia was not persistent. The insulin injections were discontinued. Subsequently, her urinary c-peptide level dramatically recovered to 81.3-87.0 μg/day, and although her glucose improved, a 75 g oral glucose tolerance test revealed an impaired glucose tolerance pattern. The details of her oral glucose tolerance test were as follows; at time points 0, 30, 60, 90, and 120 minutes, her plasma glucose levels were 116, 193, 246, 230, and 172 mg/dL, respectively, her insulin levels were 5.7, 22.4, 35.5, 46.3, and 48.6 μU/mL, respectively. Moreover, her urine catecholamine level almost completely normalized (Table 2), and postoperative MIBG scintigraphy revealed no accumulation of MIBG. At day 26 after surgery, she was discharged with no medication. Fig. 4 shows the clinical course during hospitalization. At follow-up, 10 years after surgery, there was no evidence of recurrence, including malignant pheochromocytoma, or any occurrence of multiple endocrine neoplasia, including medullary carcinoma of the thyroid.

Discussion

This case report raises two important points. Firstly, it is rare for pheochromocytoma to present with secondary diabetes mimicking insulin-dependent diabetes mellitus. Secondly, it is equally rare for the ectopic secretion of somatostatin in pheochromocytomas in conjunction with catecholamine oversecretion. Therefore, in this case, not only catecholamine, but also somatostatin is considered to have contributed to the aggravation of the glucose metabolism.

Although pheochromocytoma is one of the rare and predominant endocrine diseases that induce secondary diabetes or secondary hypertension, its accurate epidemiological frequency remains to be elucidated. According to previous reports, Beard et al. reported that the annual incidence of pheochromocytoma is approximately 0.8 per 100,000 person-years (7). La Batide-Alanore et al. reported that approximately one-third patients with pheochromocytoma are complicated with diabetes (2). Furthermore, diabetic ketoacidosis (DKA) is occasionally a fatal disease; thus, in cases of DKA, clinicians should identify and treat the underlying cause more quickly. In this case, although high glucose and diabetic ketosis were evident but not DKA, the initial differential diagnosis and treatment were therefore almost same as

Table 2. **Urine Catecholamine, and C-peptide Levels.**

Urine Catecholamine	Pre-surgery	Post-surgery	Normal range
Noradrenaline	354 and 364	177 and 119	(29–151)μg/day
Adrenaline	807 and 819	10 and 5	(2–31) μg/day
Dopamine	849 and 780	599 and 479	(282–1,002) μg/day
Metanephrine	5.31 and 6.18	0.28 and 0.19	(0.04–0.18) mg/day
Normetanephrine	1.09 and 1.31	0.08 and 0.05	(0.1–0.28) mg/day
Urine c-peptide			
Pre-surgery	**Post-surgery**		**Normal range**
5.5 [2,510 mL/day]	81.3[2,052 mL/day]		(40–100)(μg/day)
9.0 [2,190 mL/day]	87 [1,510 mL/day]		

[ ] = Urine volume/day

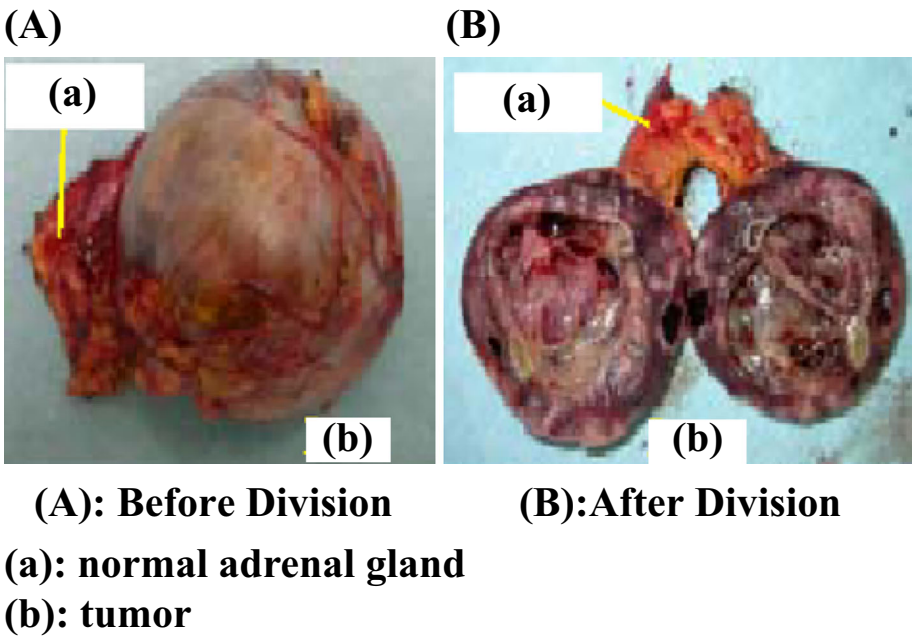

Figure 2. **Macroscopic findings of the resected tumor. Image showing a tumor measuring 5.0×5.0×5.5 cm. The divided surface is brown with a serum-like fluid present and the border of normal and tumor tissue is clearly recognized.**

for DKA. A Medline search indicated that there are some reports of DKA associated with pheochromocytoma, although the frequency was low (8). Therefore, clinicians should consider the possibility of pheochromocytoma in cases of diabetes, diabetic ketosis, and DKA.

Catecholamines are generally postulated to influence both insulin secretion and resistance in the patients with pheochromocytoma. In general, catecholamines inhibit insulin secretion via α2 receptors in the pancreas (9-11), accelerate glucagon secretion via β or α1 receptors, decrease glucose utilization in skeletal muscle, accelerate fat metabolism in fat tissue, glycogenolysis and gluconeogenesis in the liver via β2 receptors (12). A decreased insulin secretion is considered the main source of glucose metabolism disorder in pheochromocytoma (13); however, the occurrence of insulin resistance in pheochromocytoma is currently considered to be an important factor (14). In this case, the evaluation in urinary c-peptide level revealed that there was an extremely decreased insulin secretion level before surgery, which recovered after surgery. Therefore, we effectively excluded the possibility of other disorders of decreased insulin secretion, including type 1 diabetes mellitus, pancreatic diabetes, mitochondrial diabetes, and maturity-onset diabetes of the young, which made it possible to make the diagnosis of secondary diabetes due to adrenal pheochromocytoma. Unfortunately, an accurate evaluation of insulin resistance, such as using a euglycemic-hyperinsulinemic clamp, was not performed, and the-coexistence of insulin resistance was not determined.

Hypoglycemia has been reported after the removal of pheochromocytoma (15), and in particular, rebound insulin secretion has been reported (16). Moreover, pheochromocytomas that predominantly secrete adrenaline have a greater affinity to α2 receptors, thus making the possibility of rebound secretion of insulin to likely be high in this case. Therefore, we were vigilant for hypoglycemia; however, although postoperative hypoglycemia occurred, only a small dose of glucose was required and hypoglycemia was not persistent.

When considering the causes for a dramatic decrease in the insulin secretion level, we considered the importance of

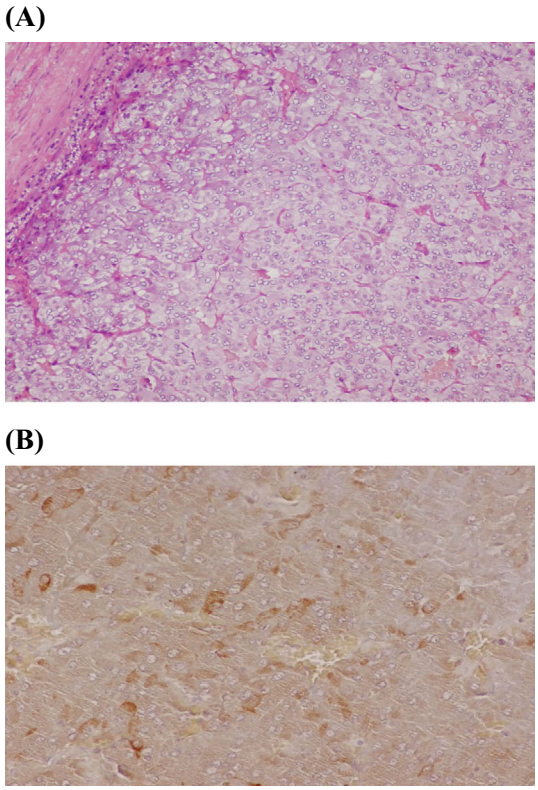

Figure 3. Pathological findings of the resected specimen. (A) Histological examination by Hematoxylin and Eosin staining showing proliferative tumor cells in the so-called "zellballen" pattern, mimicking adrenal medullary cells (high-power micrograph). (B) Most tumor cells are immunoreactive for somatostatin.

adrenaline as the predominant catecholamine in this case. Porte et al. (9, 10) reported that adrenaline has a greater suppressive effect on insulin secretion than noradrenaline because of the higher affinity of α2-receptors in the pancreas. In addition, La Batide-Alanore et al. (2) reported that the plasma adrenaline concentrations in patients with pheochromocytoma were higher in 68 patients with diabetes when compared with those in than 123 patients without diabetes. In contrast, Turnbull et al. (1) reported that α-adrenergic blockade alone or together with β-blockade restored the insulin response to glucose but failed to correct glucose intolerance in the oral glucose tolerance test in a patient with pheochromocytoma. In this study, although the total amount of insulin reduced by approximately 20% from the maximum dose after administering α- and β-adrenergic blockade, 38 U/day insulin was still necessary to maintain glycemic control. Regarding this point, Turnbull et al. (1) reported that the residual glucose intolerance after adrenergic blockade may result from an incomplete blockade or factors other than α- and β-adrenergic activity. Despite adequate adrenergic blockade in our patient, the total dose of insulin remained high; therefore, we considered the possibility of another diabetic mechanism, such as simultaneous hormone secretion, as being the cause.

Another reason that considered for a dramatic decrease in the insulin secretion levels was the possibility of glucose toxicity at the time of measuring urinary c-peptide levels. Although glucose toxicity is defined by a decrease in insulin secretion due to chronic high glucose, several facts remain unclear, including what constitutes the absolute plasma glucose level, the period required for chronicity, and the point at which glucose toxicity ends. Recently, it was reported that the ability to secrete insulin diminished in patients with BMI of <20 kg/m^2, and >25 kg/m^2 but with a high HbA1c level (>10%) in Japanese patients with type 2 diabetes and that HbA1c level of >10% was related to glucose toxicity (17). However, the relationship between glucose toxicity and pheochromocytoma remains unclear. In this case, although the glucose and HbA1c levels were both initially elevated, by the time the urinary c-peptide level was measured at 3 weeks after the initiation of insulin therapy, the casual blood glucose level was in the range of 100-200 mg/dL and ketonuria had disappeared. Furthermore, there was a significant fluctuation in blood sugar levels, and hypoglycemia had already occurred. Therefore, we considered that it was unlikely that glucose toxicity had caused a false low urinary c-peptide level in this case.

In addition, we considered the possibility of simultaneous hormone secretion, specifically with somatostatin, as a cause for the decreased insulin secretion. Currently, it is known that various hormones, such as somatostatin, vasoactive intestinal peptide, adrenocorticotropic hormone, and interleukin-6 can be secreted by pheochromocytomas (3, 18, 19). Somatostatin is mainly secreted by D cells in the pancreas and it is known to inhibit insulin and glucagon to induce diabetes (5, 20, 21). Therefore, we immunohistochemically evaluated the residual specimen and found the tumor to be positive for somatostatin, thereby indicating that this hormone was secreted. This was supported by the high level of somatostatin in the fluid of the isolated tumor. However, unfortunately, we did not measure the somatostatin level in the peripheral blood before surgery.

Somatostatin suppresses the secretion of both insulin and glucagon; therefore, in our patient, the suppression of insulin secretion might have influenced the onset of diabetic ketosis. Although the physiological role of glucagon has not yet been completely elucidated, the possible mechanisms leading to diabetic ketosis or ketoacidosis are as follows: 1) glucagon promotes gluconeogenesis in the liver, which elevates plasma glucose and 2) glucagon promotes lipolysis in the adipose tissues, which promotes ketone production. Therefore, if glucagon secretion was suppressed, as a result, which might inhibit pathophysiology of diabetic ketosis (22). Unfortunately, in our patient, we could not measure the serum level of glucagon in the state of diabetic ketosis, and therefore, glucagon's effect on diabetic ketosis remains unclear.

The first reported case of a somatostatin-producing neuroendocrine tumor was in 1977 (20, 21), and since then, over 200 cases have been reported regarding neuroendocrine tumors (23). In this study, there was no evidence of a

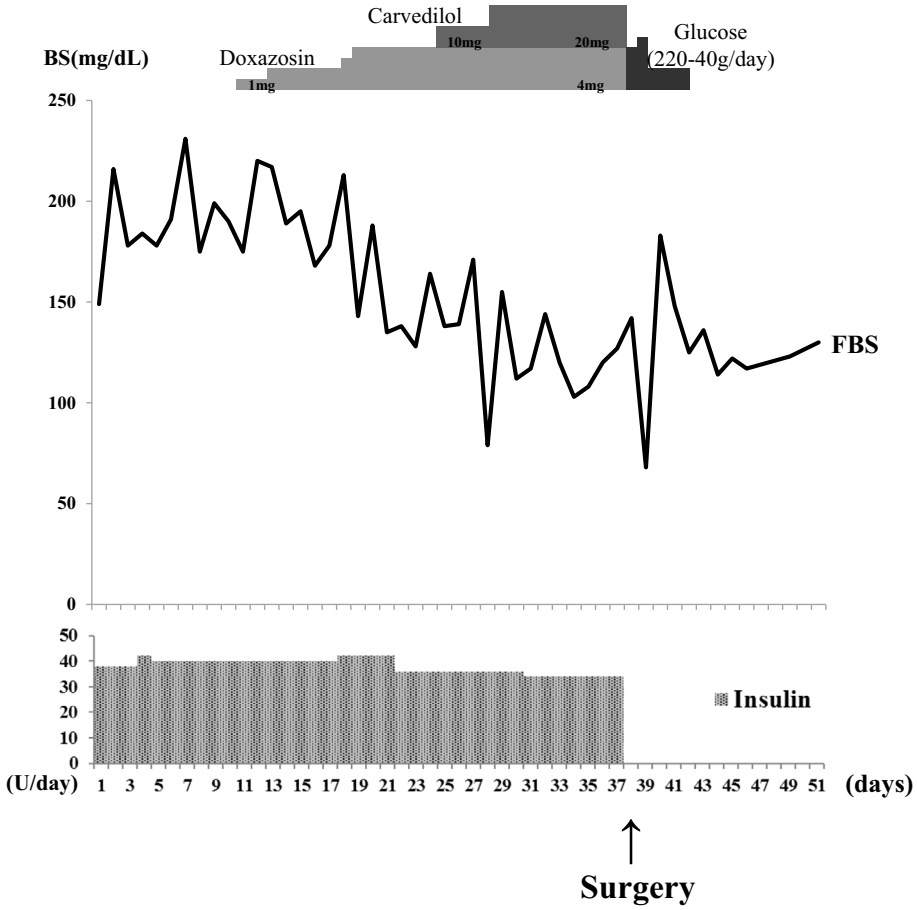

Figure 4. Clinical Course. The clinical course of fasting blood glucose is shown; on admission, Humulin R (10-10-10) and Humulin N (0-0-0-10) was continued from the previous hospital and adjusted as shown. Doxazosin 1 mg was initiated on day 10 of admission and carvedilol 10 mg was initiated on day 25, reaching the final doses of 4 mg and 20 mg, respectively, before surgery. On day 38, laparoscopic adrenalectomy was performed and the adrenal tumor removed. After surgery, 4-10 % glucose was administrated for 5 days and the insulin and adrenergic blockers were discontinued. FBS: fasting blood sugar

neuroendocrine tumor, including multiple endocrine neoplasia. Although the typical symptoms of excess somatostatin secretion include diarrhea, cholelithiasis, achlorhydria, and diabetes (the so called "somatostatinoma syndrome", described by Krejs in 1979) (24), such manifestations are rare and many previous cases are reported to be asymptomatic. It is believed that this is because very high serum somatostatin levels are necessary to cause these symptoms. In this case, the symptoms of somatostatin excess were unclear, which is consistent with the few cases of somatostatin-secreting pheochromocytomas reported in the literature (3, 6, 25, 26), Although Sano et al. (3) reported that a 50-g glucose-tolerance test showed the pattern of diabetes mellitus and the level of measured somatostatin in their case of somatostatin-secreting pheochromocytoma, other such cases predominantly reported immunostaining of somatostatin and not about diabetes (6, 25). Therefore, the exact proportion of patients with somatostatin-secreting pheochromocytoma that present with hyperglycemia remains unknown. In this case, although we consider that the evidence is consistent with simultaneous somatostain-secreting pheochromocytoma, unfortunately, we did not measure serum somatostatin level in the peripheral blood before surgery; therefore, we could not be certain how somatostatin influenced insulin secretion. However, given the extremely low urinary c-peptide level, we consider that both catecholamine and somatostatin excess probably aggravated the glucose metabolism disorder. Consequently, a very low insulin secretion was characteristic in this case, in comparison to previous cases of somatostatin-secreting pheochromocytoma. Therefore, clinicians should consider coproductive hormones including somatostatin as seen in our case. To the best of our knowledge, we are the first to report a patient with a somatostatin-secreting pheochromocytoma associated with a dramatic decrease in insulin secretion that mimicked type 1 diabetes mellitus.

Recently, the importance of genetic testing in the diagnosis of pheochromocytomas and paragangliomas (PPGLs) is being widely recognized. Lenders et al., in their review (2014) of genetic testing in PPGLs so far (27), recommend that all patients with PPGLs should be engaged in shared decision making for genetic testing. The reasons are as follows: 1) at least one-third of all patients with PPGLs have

disease-causing germline mutations; 2) mutations of succinate dehydrogenase complex subunit B (SDHB) lead to metastatic disease in 40% or more of affected patients; and 3) establishing a hereditary syndrome in the proband may result in an earlier diagnosis and treatment of PPGLs and other syndromic manifestations among relatives. Unfortunately, although we could not obtain informed consent for to undergo genetic testing from our patient, she had fortunately no evidence of hereditary syndrome at the 10-year follow-up after surgery. However, genetic testing in PPGLs might become more common and important in the future; thus, when encountered cases of PPGLs, clinicians should actively consider genetic testing.

In summary, clinicians should be aware of the possibility of simultaneous hormone secretion in patients with pheochromocytoma, particularly of somatostatin secretion, when the patients present with symptoms mimicking insulin-dependent diabetes mellitus.

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

The authors state that they have no Conflict of Interest (COI).

References

1. Turnbull DM, Johnston DG, Alberti KG, et al. Hormonal and metabolic studies in a patient with a pheochromocytoma. J Clin Endocrinol Metab **51**: 930-933, 1980.
2. La Batide-Alanore A, Chatellier G, Plouin PF. Diabetes as a marker of pheochromocytoma in hypertensive patients. J Hypertens **21**: 1703-1707, 2003.
3. Sano T, Saito H, Inaba H, et al. Immunoreactive somatostatin and vasoactive intestinal polypeptide in adrenal pheochromocytoma. An immunochemical and ultrastructural study. Cancer **52**: 282-289, 1983.
4. Ling N, Burgus R, Rivier J, et al. The use of mass spectrometry in deducing the sequence of somatostatin--a hypothalamic polypeptide that inhibits the secretion of growth hormone. Biochem Biophys Res Commun **50**: 127-133, 1973.
5. Kim DM, Ahn CW, Kim KR, et al. Duodenal somatostatinoma associated with diabetic ketoacidosis presumably caused by somatostatin-28 hypersecretion. J Clin Endocrinol Metab **90**: 6310-6315, 2005.
6. Gong J, Wang X, Chen X, et al. Adrenal and extra-adrenal nonfunctioning composite pheochromocytoma/paraganglioma with immunohistochemical ectopic hormone expression: comparison of two cases. Urol Int **85**: 368-372, 2010.
7. Beard CM, Sheps SG, Kurland LT, Carney JA, Lie JT. Occurrence of pheochromocytoma in Rochester, Minnesota, 1950 through 1979. Mayo Clin Proc **58**: 802-804, 1983.
8. Douma S, Petidis K, Kartali N, Mahera K, Sabanis C, Zamboulis C. Pheochromocytoma presenting as diabetic ketoacidosis. J Diabetes Complications **22**: 295-296, 2008.
9. Porte D Jr, Williams RH. Inhibition of insulin release by norepinephrine in man. Science **152**: 1248-1250, 1966.
10. Porte D Jr, Graber AL, Kuzuya T, et al. The effect of epinephrine on immunoreactive insulin levels in man. J Clin Invest **45**: 228-236, 1966.
11. Isles CG, Johnson JK. Phaeochromocytoma and diabetes mellitus: further evidence that alpha 2 receptors inhibit insulin release in man. Clin Endocrinol (Oxf) **18**: 37-41, 1983.
12. Cryer PE. Adrenaline: a physiological metabolic regulatory hormone in humans? Int J Obes Relat Metab Disord **17**: S43-S46; discussion S68, 1993.
13. Hamaji M. Pancreatic alpha- and beta-cell function in pheochromocytoma. J Clin Endocrinol Metab **49**: 322-325, 1979.
14. Wiesner TD, Blüher M, Windgassen M, et al. Improvement of insulin sensitivity after adrenalectomy in patients with pheochromocytoma. J Clin Endocrinol Metab **88**: 3632-3636, 2003.
15. Wilkins GE, Schmidt N, Doll WA. Hypoglycemia following excision of pheochromocytoma. Can Med Assoc J **116**: 367-368, 1977.
16. Akiba M, Kodama T, Ito Y, et al. Hypoglycemia induced by excessive rebound secretion of insulin after removal of pheochromocytoma. World J Surg **14**: 317-324, 1990.
17. Ohkura T, Fujioka Y, Izawa S, et al. Endogenous insulin secretion ability in meal tolerance test correlated with body mass index (BMI) in Japanese type 2 diabetes patients. Int J Diabetes Dev Ctries **34**: 193-200, 2014.
18. Kang JM, Lee WJ, Kim WB, et al. Systemic inflammatory syndrome and hepatic inflammatory cell infiltration caused by an interleukin-6 producing pheochromocytoma. Endocr J **52**: 193-198, 2005.
19. Sato M, Watanabe T, Ashikaga T, et al. Adrenocorticotropic hormone-secreting pheochromocytoma. Intern Med **37**: 403-406, 1998.
20. Larsson LI, Hirsch MA, Holst JJ, et al. Pancreatic somatostatinoma. Clinical features and physiological implications. Lancet **26**: 666-668, 1977.
21. Ganda OP, Weir GC, Soeldner JS, et al. "Somatostatinoma": a somatostatin-containing tumor of the endocrine pancreas. N Engl J Med **296**: 963-967, 1977.
22. Gerich JE, Lorenzi M, Bier DM, et al. Prevention of human diabetic ketoacidosis by somatostatin. Evidence for an essential role of glucagon. N Engl J Med **292**: 985-989, 1975.
23. Sugiyama T, Nakanishi M, Hoshimoto K, et al. Severely fluctuating blood glucose levels associated with a somatostatin-producing ovarian neuroendocrine tumor. J Clin Endocrinol Metab **97**: 3845-3850, 2012.
24. Krejs GJ, Orci L, Conlon JM, et al. Somatostatinoma syndrome. Biochemical, morphologic and clinical features. N Engl J Med **301**: 285-292, 1979.
25. Saito H, Saito S, Sano T, et al. Immunoreactive somatostatin in catecholamine-producing extra-adrenal paraganglioma. Cancer **50**: 560-565, 1982.
26. Wilson RB, Holscher MA, Kasselberg AG, et al. Leu-enkephalin and somatostatin immunoreactivities in canine and equine pheochromocytomas. Vet Pathol **23**: 96-98, 1986.
27. Lenders JW, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab **99**: 1915-1942, 2014.