Somatostatin-secreting Pheochromocytoma Mimicking Insulin-dependent Diabetes Mellitus

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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

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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
As shown in Table 2, a high catecholamine level demonstrated an accumulation in this right adrenal tumor and 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 catecholamine 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 dosage of 2-8 mg/day. In parallel, doxazosin was administered at a dosage of 2-8 mg/day.

Table 1. Laboratory Data on Admission.

| Parameter    | Result   | Unit | Parameter      | Result   | Unit |
|--------------|----------|------|---------------|----------|------|
| WBC          | 5,600    | /μL  | Na            | 139      | 138-146 /mEq/L |
| RBC          | 416 (366-478) | /μL | K             | 4.8      | 3.6-4.9/mEq/L |
| Hb            | 13.2 (11.6-14.0) | g/dL | CI            | 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) | /μL | Cre           | 0.60     | 0.40-0.70/mg/dL |
| TP            | 6.5 (6.7-8.3) | g/dL | Cl            | 40       | 45-163/IUL |
| Alb           | 3.8 (5.9-4.9) | 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     | <0.30-0.30/mg/dL |
| AIP           | 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 | U-Glucose     | 142      | <4+       |
| ACTH          | 7.08 (7.20-63.3) | pg/mL | U-Protein     | 4.4      | <4+       |
| Cortisol      | 9.48 (6.20-19.4) | μg/dL | U-Ketone      | 518      | <4+       |
| DHEA-S        | 518 (210-120) | ng/ml |                 |          |       |
| PRA           | 2.18 (0.30-2.90) | mg/mL/hr | U-Blood       | 142      | <4+       |
| ALD           | 142 (29.9-159) | pg/mL |                 |          |       |
| CEA           | 4.4 (<4.9) | ng/mL |                 |          |       |
| Calcitonin    | 14.0 (<6.2) | pg/mL |                 |          |       |

AChT: adrenocorticotropic hormone, Alb: albumin, A1D: Aldosterone, AIP: 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.

Parameter Result Unit Parameter Result Unit

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|-----------|--------|------|-----------|--------|------|
| WBC       | 5,600  | /μL  | Na        | 139    | 138-146 /mEq/L |
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| ALT       | 18     | IU/L | HDL-C    | 60     | 49-74/mg/dL |
| LDH       | 197    | IU/L | CRP      | 0.30   | <0.30-0.30/mg/dL |
| AIP       | 113    | IU/L |           |        |       |
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| Calcitonin| 14.0   | pg/mL |           |        |       |
A 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, 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] |                       |

[A] = 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.

(A): Before Division  
(b): tumor

(B): After Division

(a): normal adrenal gland

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, glycolysis 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
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
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 somatostatin-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 co-productive 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 be considered in 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).

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