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CASE

A case of pheochromocytoma complicated with slowly progressive type 1 diabetes mellitus and chronic thyroiditis

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Abstract This is a case report regarding a 45-year-old woman, who has been undergoing treatment for diabetes mellitus (DM) with chronic thyroiditis (euthyroid state). The patient was admitted to our hospital for the evaluation of a right adrenal tumor (50 × 45 mm) and episodic hypertension. She was diagnosed as having pheochromocytoma based on the increased catecholamine and metabolite concentrations and the result of iodine-131 metaiodobenzyl guanidine (^{131}I-MIBG) scintigraphy. Subsequently, the right adrenal tumor was excised. Slowly, progressive type 1 DM (SPIDDM) was confirmed by seropositivity to anti-glutamic acid decarboxylase (1890 U/ml) and the clinical course. After right adrenalectomy, the elevated catecholamine and metabolite concentrations and blood pressure retuned to normal, and the dosage of insulin injection was reduced. However, she still needed the insulin injection therapy to control her blood glucose level. This case exhibited an extremely rare combination of pheochromocytoma and SPIDDM with chronic thyroiditis. Although it is common for patients with pheochromocytoma to exhibit glucose intolerance, this case raises the suggestion that measuring the levels of the autoantibody for pancreatic islet cells should be considered if SPIDDM is suspected in a patient with pheochromocytoma.

Keywords Anti-glutamic acid decarboxylase antibody · Pheochromocytoma · Chronic thyroiditis · Slowly progressive type 1 diabetes mellitus · Hypertension

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Introduction

Pheochromocytoma is a tumor that produces catecholamine [1, 2]. Thus, catecholamine hypersecretion is a common clinical manifestation of the tumor. Pheochromocytoma is an insidious disease. Due to the paucity of signs and symptoms in some patients, glucose intolerance and/or hyperglycemia occurs in up to one-third of these patients, and hypertension complicating the course of diabetes is common. Many patients with pheochromocytoma are not diagnosed pre-mortem [3]. Slowly progressive type 1 (insulin-dependent) diabetes mellitus (SPIDDM) is a disease in which diabetes mellitus (DM), after an initial non-insulin-dependent stage, progresses to an insulin-dependent state as a result of a gradual decrease in insulin secretion and the presence of autoantibodies for pancreatic islet cells. SPIDDM is known to often accompany other autoimmune diseases [4] but not pheochromocytoma. Here, we report a case in which pheochromocytoma was observed during the follow-up to SPIDDM.

Case report

A 45-year-old woman was transferred to our hospital for the evaluation of a right adrenal tumor and episodic

hypertension. The patient complained of general fatigue and was diagnosed with DM. Medication was started, and insulin therapy was initiated the following year. Her family history was unremarkable. On admission, her physical findings were normal. She was 158.6-cm tall and weighed 55.8 kg. Blood pressure was 130/68 mmHg, and heart rate was normal sinus rhythm. The results of laboratory investigations, including those of routine blood test, for measuring electrolytes, enzymes, and chemistry, were within normal limits (data not shown). Preoperative basal hormonal values are shown in Table 1. Increased levels of plasma adrenaline and noradrenaline, urine adrenaline, noradrenaline, metanephrine, normetanephrine, and vanillymandelic acid were detected. An abdominal computed tomography (CT) scan showed a mass on the right adrenal gland (measuring 50 × 45 mm), which was round, well defined, and non-calcified (Fig. 1a). A whole-body scan using iodine-131 metaiodobenzyl guanidine (^{131}I-MIBG) revealed an evident accumulation of ^{131}I only over the right adrenal gland (Fig. 1b). Thus, the adrenal tumor was clinically diagnosed as pheochromocytoma.

Table 1 Endocrinological data on admission

	Value	Normal range
Thyroid stimulating hormone (TSH)	1.4 μIU/ml	(0.35–3.7 μIU/ml)
Free triiodothyronine	2.8 pg/ml	(2.20–4.20 pg/ml)
Free thyroxine	1.2 ng/ml	(0.88–1.81 ng/ml)
Thyroid test	<100	(<100)
Thyroid peroxidase antibody	28.4 U/ml	(<0.3 U/ml)
Hemoglobin A 1c	8.7%	(4.3–5.8%)
Urinary C-peptide	36.1 μg/day	(40–100 μg/day)
Immunoreactive insulin	5 μU/ml	(2.4–23.2 μU/ml)
Anti-glutamic acid decarboxylase	1890 U/ml	(<5 U/ml)
Islet cell antibody	(–)	(–)
Insulin antibody	12%	(7%)
Adrenocorticotropin (ACTH)	32 pg/dl	(9–52 pg/dl)
Cortisol	9.6 μg/dl	(4–18.3 μg/dl)
Plasma renin activity	2.5 ng/ml/h	(0.2–2.7 ng/ml/h)
Aldosterone	134 pg/ml	(56.9–150.3 pg/ml)
Adrenaline	0.31 ng/ml	(<0.1 ng/ml)
Noradrenaline	0.60 ng/ml	(0.1–0.45 ng/ml)
Dopamine	0.01 ng/ml	(<0.02 ng/ml)
Urine		
Adrenaline	154.5 μg/day	(3.4–26.9 μg/day)
Noradrenaline	240.7 μg/day	(48.6–168.4 μg/day)
Dopamine	711.3 μg/day	(365–961 μg/day)
Metanephrine	2.93 mg/day	(0.04–0.19 mg/day)
Normetanephrine	1.04 mg/day	(0.09–0.33 mg/day)
Vanillymandelic acid	7.70 mg/g Cr	(1.5–4.3 mg/g Cr)

The patient's fasting blood glucose level was 226 mg/dl and hemoglobin A1c (HbA1c) was 8.7%. Islet cell antibodies were not detected; 12% of insulin antibody and a high titer (1890 U/ml) of anti-glutamic acid decarboxylase antibody (GAD) were detected (Table 1). The findings of the clinical course resulted in a diagnosis of SPIDDM. Thyroid function tests showed normal levels of thyroid stimulating hormone (TSH), free triiodothyronine, and free thyroxine. The serum levels of thyroid peroxidase antibody and the results of the thyroid test were high. Ultrasound examination of the thyroid gland revealed a diffuse enlargement of the thyroid gland with reduced and inhomogenous echogeneity, confirming the diagnosis of chronic thyroiditis. The patient was diagnosed as having SPIDDM with chronic thyroiditis.

Pretreatment with an α-adrenergic blocker can usually be undertaken and is safe for most patients even if they are hypotensive and not hypertensive [5]. In this case, the α-adrenergic antagoist doxazosin was administered in increasing doses from 0.5 mg to a mild dose of 4 mg once a day to increase the circulating blood volume, although the patient's blood pressure remained below 120/80 mmHg. This treatment normalized the central venous pressure (approximately 5 cmH_2O). The patient underwent laparoscopic right adrenalectomy. The tumor in the excised sample was revealed to be 50 × 45 mm in diameter, soft, and with a white cut surface; it had some necrotic tissue internally. Histopathological findings (Fig. 2) of the tumor presented a solid proliferation of small round cells that stained positive with chromogranin A. The diagnosis of pheochromocytoma was confirmed on histological examination. After right adrenalectomy, the elevated catecholamine and metabolite concentrations retuned to normal (Table 2). The effects of catecholamines from the pheochromocytoma on insulin secretion or resistance could not be estimated because we could not perform hyperglycemic and euglycemic clamp techniques. However, the patient's FBS and HbA1c were improved after the operation despite a reduced dosage of insulin injection; however, she still needed the insulin injection therapy to control her blood glucose level (Fig. 3). On annual follow-up for 2 years, the catecholamine and metabolite concentrations in the plasma and urine have been normal. Abdominal CT has demonstrated no abnormal masses.

Discussion

The true incidence of pheochromocytoma is not well known. In one study, 0.13% of autopsies of the general population revealed pheochromocytoma and it is estimated

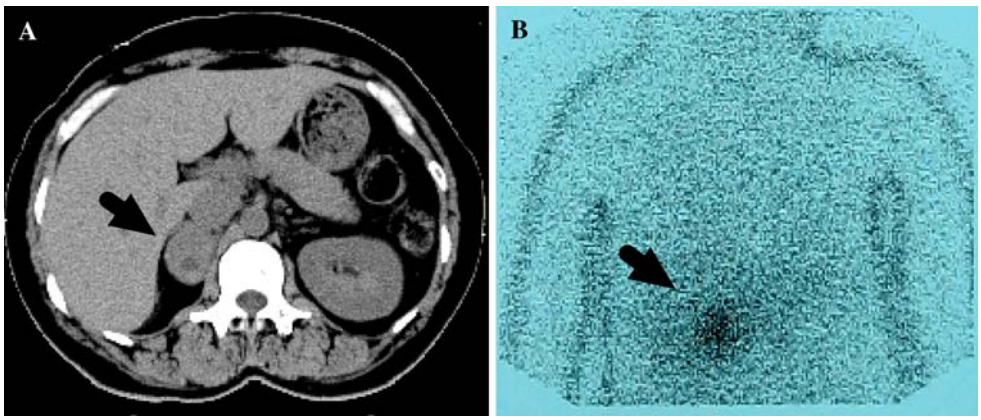

Fig. 1 (**a**) Computed tomography (CT) of the abdomen demonstrates a 50 × 45 mm right adrenal mass. (**b**) An iodine-131 metaiodobenzyl guanidine (^{131}I-MIBG) scintigram reveals abnormal accumulation of ^{131}I in the adrenal gland

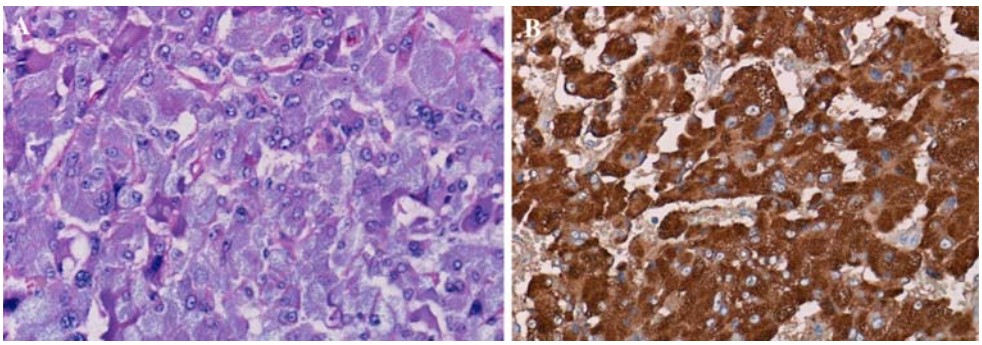

Fig. 2 Microscopic appearance of the tumor. (**a**) Small round cells with solid proliferation (HE stain, ×400), (**b**) tumor cells were positive on immunohistochemical staining (chromogranin A stain, ×400)

Table 2 Changes of hormone levels and treatment

	Pre-operative	Post-operative
Plasma		
Adrenaline (pg/ml)	310	11
Noradrenaline (pg/ml)	605	161
Dopamine (pg/ml)	16	11
Urine		
Adrenaline (μg/day)	154.5	15
Noradrenaline (μg/day)	240.7	61.2
Dopamine (μg/day)	711.3	567.2
Metanephrine (mg/day)	2.93	0.05
Normetanephrine (mg/day)	1.04	0.12
Vanillymandelic acid (mg/gCr)	7.7	2.9
Dose of insulin injection (U/day)	38	24

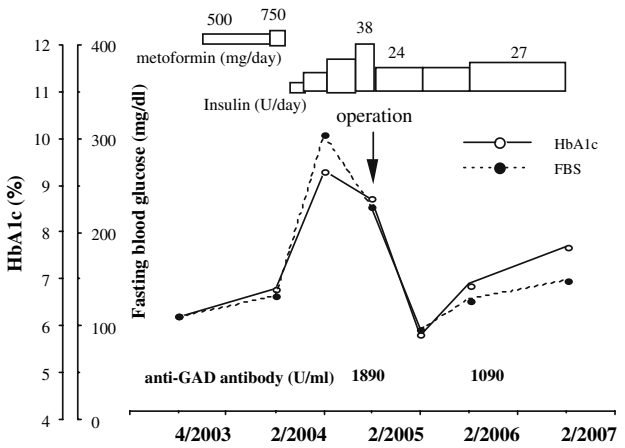

Fig. 3 Clinical course of the patient. HbA1c: hemoglobin A1c, anti-GAD antibody: anti-glutamic acid decarboxylase antibody

that less than 1% of cases with systemic hypertension are due to pheochromocytoma [1]. Although hypertension is the most common clinical finding in pheochromocytoma, it may not present in all cases. In one study of 54 autopsy-proven cases of pheochromocytoma, only 60% of the cases had been hypertensive and two-thirds had persistent hypertension and one-third had paroxysmal hypertension [1]. Other findings and associated conditions include detection of an abdominal mass, postural hypotension (50–70%), weight loss, and metabolic disturbances, particularly hyperglycemia. In a report from the Mayo Clinic regarding 76 patients with pheochromocytoma, 20% of the patients with paroxysmal hypertension and 30% of those with persistent hypertension had fasting hyperglycemia [6].

Impaired glucose tolerance was observed in patients with pheochromocytoma with an incidence of 25–75% [7]. High plasma concentrations of catecholamines inhibit the insulin response to secretagogues like sulfonylureas [8, 9]. The inhibitory effects of catecholamines on insulin

secretion [10] are adrenergic receptor mediated [11]. Reduced insulin secretion has repeatedly been reported in patients with pheochromocytoma [7, 12]. Therefore, the development of diabetes associated with pheochromocytoma is assumed to be mainly due to decreased insulin secretion. On the other hand, a recent report provides evidence that excess endogenous catecholamines in patients with pheochromocytoma can induce or aggravate insulin resistance both in patients with type 2 diabetes and patients with normal glucose tolerance [13]. The present case is another example that clearly demonstrates the association between overt clinical DM and pheochromocytoma. SPIDDM is defined as follow: [1] late onset; [2] continuously positive anti-GAD antibody, anti-IA-2 antibody, and /or anti-islet cell antibody; [3] slowly progressing of type 1 DM; and [4] possible to achieve good control of DM by using diet therapy and oral hypoglycemic agents at the early stage of onset [4]. The onset of DM in this patient was presumed to be at an advanced age. In addition, the anti-GAD antibody titer was high, and she was treated with oral hypoglycemic agents at onset. Such evidence strongly indicated that she suffered from SPIDDM. Prior to the introduction of islet auto-antibody assays, studies had shown that the level of C-peptide secretion facilitates the prediction of insulin requirement in adults presenting with diabetes [14]. Fourlanos et al. suggest that insulin independence in clinical practice is corroborated by a formal demonstration of adequate insulin production at diagnosis [15]. Evidence suggests a role of catecholamines in the regulation of the immune system. β_2-Agonists inhibit interleukin-12 (IL-12) production by monocytes and dendritic cells and inhibit the development of T helper 1 (Th1) cells [16]. A previous report demonstrated that β_2-adrenergic receptors are expressed on the surface of Th1 cells but not Th2 cells and β_2-agonists inhibit interferon-γ (INFγ) production by Th1 cells [17]. Th1 cytokines, such as INFγ, and Th1-inducing cytokines, such as IL-12, are involved in the pathogenesis of various organ-specific autoimmune diseases, including autoimmune diabetes [18]. Thus, it is conceivable that catecholamines may contribute to the production of the autoantibody for pancreatic islet cells. However, thus for, there was no direct evidence available to support this notion, because no patient with both pheochromocytoma and SPIDDM had been reported.

Slowly progressive type 1 DM is known to often accompany other autoimmune diseases [4]. Polyglandular autoimmune syndrome (PGAS) is characterized by the development of disorders in multiple endocrine and non-endocrine systems that are mediated by autoimmune mechanisms [19, 20]. There are three categories of PGAS. Types I and II develop Addison's disease, while type III does not. In addition to Addison's disease, type I is characterized by chronic mucocutaneous candidiasis and hypoparathyroidism, while type II is characterized by autoimmune thyroid disease and type 1 DM. Type III, which is characterized by autoimmune thyroid disease and the absence of Addison's disease, is accompanied by type 1 DM, pernicious anemia and vitiligo and/or alopecia [21]. The present case of SPIDDM was accompanied by chronic thyroiditis and an absence of Addison's disease, which was considered to be consistent with PGAS type III.

In conclusion, this is first report of a case of pheochromocytoma and SPIDDM with chronic thyroiditis. Our findings lead us to suggest that measuring the levels of the autoantibody for pancreatic islet cells should be considered if SPIDDM is suspected in a patient with pheochromocytoma.

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