Overt Diabetes Mellitus in a Patient with Combined Primary Aldosteronism and Cushing’s Syndrome

Nobuhiro Sasaki 1, Masanori Iwase 1, Hisatomi Arima 1, Sakae Nohara 1, Sachiko Bandai 1, Takashi Yao 2, Koji Fujii 1 and Mitsuo Iida 1

Abstract

Although there are some case reports of combined aldosterone and cortisol producing adrenal tumor, overt diabetes mellitus has been rarely described. A 55-year-old hypertensive woman had hypokalemia and overt hyperglycemia without Cushingoid clinical features. The body mass index was 18.2 kg/m², fasting blood glucose was 302 mg/dl and hemoglobin A1c was 11.6%. Endogenous insulin secretion was well preserved, whereas insulin sensitivity measured by short insulin tolerance test was markedly impaired. A solitary left aldosterone- and cortisol-producing adrenal tumor was diagnosed. We described a rare case of overt diabetes mellitus in a patient with combined primary aldosteronism and Cushing’s syndrome.

Key words : Cushing’s syndrome, insulin resistance, adrenal tumor, insulin tolerance test, hypertension

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Introduction

It is known that several hormones may be secreted from a single adrenal tumor. Aldosterone-producing tumor is a common cause of secondary hypertension (1), and may autonomously secrete cortisol as well (2, 3). Patients with such lesions lack typical Cushingoid clinical features and present only with primary aldosteronism (PA) (4). A number of investigators have termed this condition pre-Cushing type PA (4) or combined PA and preclinical Cushing’s syndrome (5). Reports of PA associated with overt Cushing’s syndrome however, are rare (6-8). Since abnormal glucose metabolism is frequently associated with PA (9) or preclinical Cushing’s syndrome (10), the combination of the two conditions could be associated with the development of overt diabetes mellitus. Here, we report a case of overt diabetes mellitus in a patient with combined PA and Cushing’s syndrome. We studied insulin secretion and sensitivity before and after the removal of the adrenal tumor.

Case Report

A 55-year-old woman was admitted to our hospital due to poorly controlled diabetes mellitus. She was found to be hypertensive at the age of 35 years and was treated with anti-hypertensive medication. Hypokalemia was pointed out at 50 years of age, but no further examinations were performed. Hyperglycemia was noted at 53 years of age, and facial nerve palsy at 54 years. She complained of thirst and blurred vision at 55 years, and visited the ophthalmology clinic at our hospital. The blood glucose after meal was 482 mg/dl and hemoglobin A1c (HbA1c) was 12.2%. Her mother had hypertension and her elderly brother had hypertension and diabetes mellitus. She was not an alcohol drinker or smoker. Height was 151 cm, body weight was 41 kg, and body mass index (BMI) was 18.2 kg/m². She reported no history of obesity (maximal BMI was 21.1 at 35 years). Arterial blood pressure was 162/96 mmHg, and pulse rate was 78 /min. Examination of the chest and abdomen showed no abnormalities except for a surgical scar from hysterectomy performed for myoma uteri at the age of 30 years. The deep tendon reflexes and monofilament sensation

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Table 1. Laboratory Data on Admission

<table>
<thead>
<tr>
<th>Urinalysis</th>
<th>Blood chemistry</th>
<th>Fasting BG</th>
<th>302</th>
<th>mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (++)</td>
<td>TP 6.5</td>
<td>g/dl</td>
<td>HbA1c 11.6 %</td>
<td></td>
</tr>
<tr>
<td>Protein (+)</td>
<td>Albumin 4.0</td>
<td>g/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketone body (-)</td>
<td>BUN 13</td>
<td>mg/dl</td>
<td>FRA 425 μmol/l</td>
<td></td>
</tr>
<tr>
<td>Occult blood (-)</td>
<td>Cr 0.7</td>
<td>mg/dl</td>
<td>Anti-GAD antibody $&lt;0.3$ μU/ml</td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td>UA 3.6</td>
<td>mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC 10160 /μl</td>
<td>T Bil 0.7</td>
<td>mg/dl</td>
<td>Renal function</td>
<td></td>
</tr>
<tr>
<td>Neutrophil 76 %</td>
<td>D Bil 0.1</td>
<td>mg/dl</td>
<td>24hr Ccr 27 ml/min</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte 19 %</td>
<td>AST 26</td>
<td>U/l</td>
<td>U Prot 0.18 g/day</td>
<td></td>
</tr>
<tr>
<td>Monocyte 4.1 %</td>
<td>ALT 31</td>
<td>U/l</td>
<td>U Alb 60.4 mg/day</td>
<td></td>
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<tr>
<td>Eosinocyte 0.5 %</td>
<td>LDH 251</td>
<td>U/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basocyte 0.4 %</td>
<td>ALP 342</td>
<td>U/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC 477×10⁴ /μl</td>
<td>γ-GT 24</td>
<td>U/l</td>
<td>Arterial blood gas analysis</td>
<td></td>
</tr>
<tr>
<td>Hb 15.1 g/dl</td>
<td>ChE 124</td>
<td>U/l</td>
<td>pH 7.476</td>
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<tr>
<td>Ht 42.9 %</td>
<td>Na 141</td>
<td>mEq/l</td>
<td>PCO₂ 50.7 mmHg</td>
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<tr>
<td>Plt 23.6×10⁴ /μl</td>
<td>K 2.5</td>
<td>mEq/l</td>
<td>PO₂ 77.0 mmHg</td>
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<tr>
<td></td>
<td>Cl 97</td>
<td>mEq/l</td>
<td>HCO₃⁻ 37.0 mmol/l</td>
<td></td>
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<tr>
<td></td>
<td>Ca 9.0</td>
<td>mg/dl</td>
<td>BE 11.5 mmol/l</td>
<td></td>
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<td></td>
<td>T chol 195</td>
<td>mg/dl</td>
<td>SO₂ 95.2 %</td>
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<td></td>
<td>TG 84</td>
<td>mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CRP 0.14</td>
<td>mg/dl</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


tests were normal, but vibratory sensation at the foot was diminished. Ophthalmoscopy showed simple background retinopathy. No signs of Cushing’s syndrome (e.g., moon face, central obesity, buffalo hump, skin thinning, acne, striae) were noted.

**Laboratory tests (Table 1)**

Urinalysis showed glycosuria and proteinuria. Peripheral blood chemistry tests revealed leukocytosis and mild polycythemia. Blood chemistry tests showed hypokalemia despite administration of 25 mg spironolactone and K replacement. Marked hyperglycemia, renal dysfunction and microalbuminuria were noted. Arterial blood gas analysis showed metabolic alkalosis.

**Endocrinological examination (Table 2)**

The upright posture test revealed marked elevation of plasma aldosterone with suppression of plasma renin activity (PRA). Morning serum cortisol was above the reference range (4.8-20.5 μg/dl) and serum cortisol at 21:00 was also above the normal limit (7.7 μg/dl), although diurnal variation of serum cortisol was seen. Morning cortisol level was not suppressed by pretreatment with 2 or 8 mg dexamethasone. Urinary excretion of free cortisol was increased, while serum dehydroepiandrosterone sulfate (DHEA-S) was reduced. Urinary C peptide excretion and glucagon load test revealed a well-preserved endogenous insulin secretion. Insulin sensitivity was evaluated by the glucose disappearance rate in the short time insulin tolerance test (Kitt), i.e., plasma glucose was measured before and 3, 6, 9, 12, 15 min after intravenous injection of regular insulin (0.1 U/kg body weight). Kitt showed a markedly low result [reported normal range, 5.03 ± 0.14 (mean (SEM) %/min), (11)].

**Imaging studies (Fig. 1)**

Computed tomography (CT) (Fig. 1A) showed left adrenal tumor of 3.5 cm in diameter and magnetic resonance imaging (MRI) (Fig. 1B) showed a fatty component in the tumor. Right adrenal showed no gross abnormalities. Adrenal scintigraphy using ¹³¹I-iodoester (6-β-iodomethyl-norchol-ester) (Fig. 1C) showed uptake on the left adrenal and inhibition of the contralateral adrenal gland. Angiography showed that the left adrenal vein trunk was slightly dilated, progressed to peripheral branch, and was compressed accurately by the tumor. Venous sampling showed that the concentrations of aldosterone and cortisol in the left adrenal vein were much higher than those in the right adrenal vein and inferior vena cava below the renal veins, respectively (aldosterone 57.002 pg/ml in the left adrenal vein, 1.842 pg/ml in the right adrenal vein, 2.445 pg/ml in the inferior vena cava below the renal veins; cortisol 182.4 μg/dl in the left adrenal vein, 31.0 μg/dl in the right adrenal vein, 26.3 μg/dl in the inferior vena cava below the renal veins).

**Cardiovascular assessment**

The electrocardiogram showed insignificant ST depression and flat T wave, whereas ultracardiography and Holter electrocardiogram showed no abnormality. Cardiac autonomic function test showed mild abnormality (coefficient of R-R interval variation at rest 1.74%, delta heart rate in deep
breathing 6.7 beats/min), whereas orthostatic hypotension was not detected. Brain MRI showed T2 prolongation lesions in bilateral white matter and diffuse brain atrophy. The intima-media thickness of the carotid artery was within the normal range, but brachial-ankle pulse wave velocity was markedly accelerated [right 3,683 cm/sec, left 3,488 cm/sec, normal 1,179±28 cm/sec (12)].

**Clinical course (Fig. 2)**

Ambulatory blood pressure monitoring showed a 24-hour mean blood pressure of 148/83 mmHg, with 149/83 mmHg in day time and 146/84 mmHg in night time (non-dipper type), when she was being treated with nicardipine 60 mg, hydralazine 150 mg, verapamil 120 mg, spironolactone 25 mg, and atenolol 25 mg. The blood glucose was controlled by basal-bolus insulin therapy (regular insulin 9 units before breakfast, 5 units before lunch, 4 units before dinner; NPH insulin 8 units before bedtime). Left adrenal tumor producing aldosterone and cortisol was diagnosed, and left adrenalectomy was performed laparoscopically. The weight of the excised tumor was 29.5 g, its size was 3.5x3.0 cm, and its cut surface was yellow. As shown in Fig. 1D, the tumor was composed of cortical-like cells containing a fine granular cytoplasm and various sized nuclei. Normal adrenal gland tissue identified at the edge of the tumor were atrophic. Mitotic figures or necrosis could not be seen. The histological diagnosis was adrenocortical adenoma.

Postoperatively, hydrocortisone was administered as replacement therapy for 2 weeks. Serum potassium was immediately normalized, spironolactone and K gluconate were discontinued and blood pressure and blood glucose were diminished. Insulin therapy and cadralazine were discontinued 3 weeks after operation. Endocrinologically (Table 2), the upright posture test with furosemide, dexamethasone suppression test, serum cortisol, DHEA-S and urinary excretion of free cortisol were normalized. Although plasma ACTH was suppressed during steroid replacement therapy, it returned to the normal range 4 months after surgery. Endogenous insulin secretion remained unchanged in urinary C peptide excretion and glucagon load test, whereas insulin sensitivity (Kitt) was almost normalized. The 75 g oral glucose tolerance test performed 4 weeks after the removal of the tumor showed a diabetes mellitus pattern with suppressed insulin secretion (plasma glucose, basal : 87 mg/dl, 30 min : 158 mg/dl, 60 min : 241 mg/dl, 90 min : 270 mg/dl, and 120 min : 234 mg/dl. Serum IRI, before : 2.2 μU/ml, 30 min : 11.6 μU/ml, 60 min : 17.1 μU/ml, 90 min : 27.8 μU/ml, and 120 min : 24.1 μU/ml; insulinogenic index 0.13). At the last clinical examination, one year after excision of the adenoma, diabetes mellitus was controlled by diet alone (HbA1c 6.7%), and blood pressure was 142/86 mmHg while on nifedipine 40 mg and atenolol 50 mg.

**Discussion**

Here, we reported a 55-year-old hypertensive woman with hypokalemia and overt hyperglycemia with a family history of hypertension and diabetes mellitus. She had chronic diabetic complications of triopathy and macroangiopathy. She also had hypertensive organ damage after 20 years’ duration
Figure 1. A. Contrast enhanced computed tomography. Arrow indicates adrenal tumor. B. Contrast enhanced magnetic resonance imaging. Arrow indicates adrenal tumor. C. $^{131}$I-Adosterone adrenal scintigraphy. D. Under high power view, the tumor is composed of cortical-like cells with fine granular cytoplasm and various sized nuclei (HE stain, ×200).

Figure 2. Clinical course.

Of hypertension. Although she was at the stage of microalbuminuria, renal dysfunction was advanced, suggesting the presence of hypertensive nephrosclerosis. Plasma aldosterone was increased and plasma PRA was suppressed during the upright posture test with furosemide load. At the same time, urinary free cortisol excretion was high, and serum cortisol was not suppressed by 2 or 8 mg dexamethasone. CT, MRI, scintigraphy, and venous hormone sampling identified a left adrenal tumor, which produced aldosterone and cortisol. Since Cushingoid clinical features were lacking in the present case, preclinical Cushing’s syndrome may be considered. However, according to the diagnostic criteria of “Disorders of adrenal hormones” Research Committee in Japan (13), preclinical Cushing’s syndrome is ruled out when the morning cortisol level is consistently increased. Therefore, the diagnosis was considered to be Cushing’s syndrome associated with PA. After successful adrenalectomy followed by steroid replacement, insulin treatment was withdrawn, and the number of antihypertensive agents was reduced. However, she was still diabetic as well as hypertensive one year later.

Concurrent secretion of aldosterone and cortisol from an adrenal adenoma has been reported as PA combined with preclinical or clinical Cushing’s syndrome. As for PA combined with preclinical Cushing’s syndrome, 14 patients have been reported in the literature. All but one (93%) were female, and their mean age was 52 years (range, 34-73 years). All tumors were adenomas, and the mean size was 2.8 cm (range, 1.7-3.8 cm) in maximum diameter. Larger aldosterone-producing adenoma may produce cortisol as well and may be associated with the development of preclinical Cushing’s syndrome. Histologically, the tumor was composed of clear cells with scattered nests of compact cells, and steroidogenic enzymes including P450 c17 (3, 4, 14, 15). Three patients (21%) had brain hemorrhage. Abe (4) suggested that patients with this subtype of PA are at an increased risk of development of cardiovascular disease. The mean fasting
insulin sensitivity was considered the pathogenetic factor.

The pathogenesis of diabetes mellitus associated with PA is related to impaired insulin secretion due to hypokalemia. However, hyperglycemia is usually mild. In our clinic, we encountered 46 patients with PA between 1976 and 1998, and 7 patients (15%) had diabetes mellitus with a mean age of 56 years, mean BMI of 27 kg/m². In 1998, we encountered 46 patients with PA between 1976 and 1998, and 7 patients (15%) had diabetes mellitus with a fasting plasma glucose of less than 130 mg/dl in each patient (17). On the other hand, the prevalence of diabetes mellitus is more common in patients with preclinical or overt Cushing’s syndrome than in those with PA. One study examining 28 patients with preclinical Cushing’s syndrome (mean age, 56 years, mean BMI, 27 kg/m²) reported a prevalence rate of diabetes mellitus of 36%, and impaired insulin sensitivity was considered the pathogenetic factor (10). In the present study, we used KTT to measure the glucose disappearance rate following intravenous insulin injection as a parameter of insulin sensitivity. KTT results correlated well with glucose disposal rates measured by the euglycemic clamp method, a golden standard to evaluate peripheral insulin resistance (18). KTT results returned to near normal range after surgery in our patient. On the other hand, endogenous insulin secretory capacity stimulated by glucagon was preserved and remained unchanged after surgery, although she had a suppressed acute insulin response to oral glucose, a typical phenotype of type 2 diabetes mellitus (19). Shimmamoto et al. (20) investigated insulin sensitivity using the euglycemic clamp technique in patients with PA, and demonstrated an enhanced insulin sensitivity associated with impaired insulin secretion. Therefore, in the present case, the insulin resistance induced by cortisol excess rather than impaired insulin secretion due to hypokalemia seems to play a major role in the pathogenesis of overt diabetes mellitus. However, the genetic trait to type 2 diabetes mellitus, suggested by a positive family history may contribute to her underlying abnormal glucose regulation.

In conclusion, we described a rare case of overt diabetes mellitus in a patient with a solitary aldosterone- and cortisol-producing adrenal tumor.

References


