Suppression of Primary Aldosteronism and Resistant Hypertension by the Peroxisome Proliferator-activated Receptor Gamma Agonist Pioglitazone

Yusuke Kashiwagi, MD, Yuji Mizuno, MD, PhD, Eisaku Harada, MD, PhD, Makoto Shono, MD, PhD, Sumio Morita, MD, Michihiro Yoshimura, MD, PhD, Mayumi Yano, MD, PhD and Hirofumi Yasue, MD, PhD

Abstract: The peroxisome proliferator-activated receptor gamma (PPAR γ) agonists have been reported to have antiproliferative and tumor-suppressive effects. We report a case of 55-year-old man with primary aldosteronism (PA) whose hyperaldosteronism was suppressed with the PPAR γ agonist pioglitazone. He had drug-resistant hypertension, hypokalemia, and diabetes mellitus. The diagnosis of PA was confirmed by the oral sodium loading test (20.5 μg/d of urinary aldosterone) and Captopril challenge test (19.5 ng/dL of plasma aldosterone). Computed tomography imaging revealed no apparent adrenal mass. The result of the posture stimulation test was consistent with the diagnosis of idiopathic adrenal hyperplasia. On administration of pioglitazone (30 mg/d) and nifedipine (40 mg/d), hypertension and hypokalemia improved and plasma aldosterone decreased for more than 6 months. The sodium loading test done after 6 months of the administration revealed the near normal results (11.2 ng/dL of plasma aldosterone and 13.1 μg/d of urinary aldosterone). The findings indicated that pioglitazone suppressed PA.

Key Indexing Terms: Aldosterone; Peroxisome proliferator-activated receptor γ; Pioglitazone; Primary aldosteronism; Resistant hypertension. **[Am J Med Sci 2013;345(6):497–500.]**

Primary aldosteronism (PA) is the most common form of endocrine hypertension because of autonomous aldosterone production from the adrenal cortex.[1,2] Patients with PA typically present with hypertension, high plasma aldosterone levels, low plasma renin activity, and varying degrees of hypokalemia. PA is commonly caused by an aldosterone producing adenoma (APA) and bilateral adrenal hyperplasia or idiopathic hyperaldosteronism (IHA) or in rare cases by unilateral adrenal hyperplasia or the inherited conditions of familiar hyperaldosteronism type I to III.[1,2] Recent studies have shown that peroxisome proliferator-activated receptor gamma (PPAR γ) agonists thiazolidinediones (TZDs), which have been widely used for treatment of type 2 diabetes,[3,4] have also antiproliferative and tumor-suppressive effects.[5,6] Moreover, PPAR γ agonists are also reported to suppress aldosterone production[7] and hypertension[8,9] in experimental studies.

From the Division of Cardiovascular Medicine (YK, YM, EH, MS, SM, HY), Kumamoto Kinoh Hospital, Kumamoto Aging Research Institute, Kumamoto, Japan; Division of Cardiology, Department of Internal Medicine (YK, MYOSHIMURA), The Jikei University School of Medicine, Tokyo, Japan; and Morinoki Clinic (MYANO), Kumamoto, Japan.

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Correspondence: Hirofumi Yasue, MD, PhD, Division of Cardiovascular Medicine, Kumamoto Kinoh Hospital, Kumamoto Aging Research Institute, 6-8-1, Yamamuro, Kita-ku, Kumamoto City 860-8518, Japan (E-mail: yasue@juryo.or.jp).

It is not known, however, whether TZDs suppress PA. We report a case of PA whose hypertension had been resistant to the combined administration of multiple antihypertensive drugs and in whom hyperaldosteronism, including hypertension, hypokalemia, and high plasma aldosterone, associated with low plasma renin activity were improved in response to the PPAR γ agonist pioglitazone. We discuss the clinical implications of this observation and the possible underlying mechanisms. This study was approved by the ethical committee of our institution, and written informed consent was obtained from the patient.

METHODS AND RESULTS (CASE REPORT)

A 55-year-old man was admitted to our hospital because of resistant hypertension and hypokalemia. He was diagnosed as hypertensive 15 years ago and had been on antihypertensive drugs for more than 10 years. He was also diagnosed with diabetes mellitus 6 years ago but had not been on antidiabetic agents. His blood pressure had gradually risen and hypokalemia also was pointed out. He was referred to our hospital on suspicion of secondary hypertension because his hypertension could not be controlled below 150 to 160/100 to 110 mm Hg despite the combined administration of 5 antihypertensive drugs (50 mg/d of eplerenone, 8 mg/d of candesartan, 40 mg/d of nifedipine, 7.5 mg/d of bisoprolol, and 1 mg/d of trichlormethiazide). He had been a smoker (1 pack/d) for more than 30 years. His father had hypertension and died of cerebral hemorrhage at the age of 49 years. His antihypertensive medications were withdrawn and replaced with slow-release 40 mg/d of nifedipine, 4 mg/d of doxazosin, and 75 mg/d of hydralazine on liberal sodium intake for confirming the diagnosis of PA,[1,2] and he was hospitalized 2 months later. On admission, physical examinations revealed an alert man with a body mass index of 23.8 kg/m^2, pulse rate of 84 beats/min, blood pressure of 162/94 mm Hg, and no edema. The chest x-ray was normal. Echocardiogram revealed concentric left ventricular (LV) hypertrophy, elevated ratio of early diastolic mitral flow velocity/early diastolic annular velocity (E/e′), and normal LV ejection fraction. Clinical data on admission are shown in Table 1. Endocrinological data revealed that plasma aldosterone concentration (PAC) was 23.4 ng/dL, plasma renin activity (PRA) was 0.2 ng/mL/hr, and PAC to PRA ratio 117 ng/dL per ng/mL/hr, cortisol 19.5 μg/dL, serum glucose 128 mg/dL, insulin 6.6 μU/mL, homeostasis model assessment–insulin resistance (HOMA-IR) 2.1, HbA1c 6.6 % and B-type natriuretic peptide 77.6 pg/mL. Urinary excretion of aldosterone was 20.5 μg/24 hours on dietary sodium intake of more than 200 mEq/d for 4 days.[2] Captopril (50 mg of Captopril given orally) challenge test showed that PAC was 19.5 ng/dL (28.3% suppression) or <30% suppression, PRA 0.8 ng/mL/hr and PAC/PRA 24.4 ng/dL per ng/mL/hr or >20 ng/dL per ng/mL/hr at 1 h after challenge.[1,2] Thus, the diagnosis of PA and type 2 diabetes mellitus was confirmed. Computed tomography (CT) revealed no

TABLE 1. Clinical data on admission

Blood chemistry		Hormone analysis	
Total protein (g/dL)	6.4 (6.5–8.2)	PAC (ng/dL)	23.4 (3.6–24.0)
Albumin (g/dL)	4.1 (4.1–5.1)	PRA (ng/mL/hr)	0.2 (0.3–2.9)
Total bilirubin (mg/dL)	1.0 (0.3–1.1)	PAC/PRA (ng/dL per ng/mL/hr)	117
AST (U/L)	15 (13–34)	ACTH (pg/mL)	36.5 (7.2–63.3)
ALT (U/L)	9 (7–37)	Plasma cortisol (μg/dL)	19.5 (4–18.3)
LDH (U/L)	185 (112–213)	Urinary aldosterone (μg/d)	20.5 (≦10)
Urea nitrogen (mg/dL)	21.5 (8.4–21.0)	TSH (μIU/mL)	0.8 (0.34–4.22)
Creatine kinase (mg/dL)	0.9 (0.6–1.2)	Free T3 (pg/mL)	3.35 (2.24–3.94)
Sodium (mEq/L)	146 (138–147)	Free T4 (ng/mL)	0.91 (0.77–1.59)
Potassium (mEq/L)	3.4 (3.5–5.0)	BNP (pg/mL)	77.6 (≦18.4)
Chloride (mEq/L)	108 (99–109)	Urinalysis	
Calcium (mg/dL)	9.5 (8.3–10.4)	pH	6.5 (4.5–8)
Magnesium (mg/dL)	2.3 (1.9–2.4)	Specific gravity	1.013 (1.002–1.030)
Glucose (mg/dL)	128 (72–110)	Protein	— (—)
Insulin (μU/mL)	6.6 (5.0–15)	Glucose	— (—)
HemoglobinA1c (NGSP) (%)	6.2 (4.3–5.8)	Occult blood	— (—)
Triglyceride (mg/dL)	97 (30–150)	Urobilinogen	± (±)
HDL-C (mg/dL)	45 (40–108)	Bilirubin	— (—)
LDL-C (mg/dL)	62 (65–139)	Arterial gas analysis	
Blood count		pH	7.443 (7.360–7.440)
White blood cells (per μL)	7200 (3900–9200)	pCO_2 (mm Hg)	42.7 (35.0–45.0)
Red blood cells ($\times 10^4/\mu L$)	429 (430–550)	pO_2 (mm Hg)	81.8 (80.0–100.0)
Hemoglobin (g/dL)	13.8 (13.5–17.0)	HCO_3 (mEq/L)	28.6 (20.1–29.0)
Hematocrit (%)	40.3 (40–50)	Base excess (mEq/L)	3.9 (−2.3 to 2.3)
Platelets ($\times 10^4/\mu L$)	23.2 (11–35)		

NGSP, The national glycohemoglobin standarization program; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone ; T3, triiodothyronine; T4, thyroxine; BNP, brain natriuretic peptide ; ( ), normal range.

apparent adrenal tumor. Adrenal vein sampling was done to distinguish between unilateral and bilateral disease. Aldosterone and cortisol levels were 1181 ng/dL and 304 μg/dL, respectively, in the left adrenal vein and 46.4 ng/dL and 30.6 μg/dL, respectively, in the left iliac vein, 15 to 20 minutes after bolus injection of 250 μg of adrenocorticotropic hormone (ACTH). Catheterization into the right adrenal vein was not successful. The posture stimulation test showed that PAC increased (from 18 ng/dL to 21 ng/dL) after standing for 2 hours.[1,10] ACTH stimulation on dexamethasone suppression test revealed that PAC decreased (from 31 ng/dL to 16 ng/dL), whereas plasma cortisol concentration increased (from 0.9 μg/dL to 23 μg/dL) 1 h after ACTH injection.[11] The results of these tests were consistent with the diagnosis of IHA, although unilateral APA subtype of PA could not be completely excluded.[1,10,11] We recommended medical treatment to the patient on these findings with his consent. We added 30 to 45 mg/d of the TZD pioglitazone to his antihypertensive medications (nifedipine, doxazosin, and hydralazine) and followed his clinical course, including blood pressure, body weight, and laboratory data, for more than 6 months. Mineralocorticoid receptor (MR) antagonists were not attempted with pioglitazone administration because eplerenone had been used in combination with other antihypertensive drugs before the admission and might have confounded the effect of pioglitazone. Blood pressure decreased and serum potassium became increased concomitant with decreases of PAC one month after pioglitazone administration. Hypertension and hypokalemia remained improved for more than 6 months, and the oral sodium loading test done 6 months after pioglitazone was almost normalized (11.2 ng/dL of PAC and 13.1 μg/24 hr of urinary aldosterone. Body weight increased from 58 kg to 61 kg after one month of pioglitazone and remained stable thereafter. Echocardiographic LV mass and E/e′ decreased, and LV ejection fraction increased, indicating that cardiac hypertrophy and function improved after pioglitazone administration. These results are shown in Table 2. However, the adrenal CT imaging remained almost unchanged after pioglitazone administration.

DISCUSSION

PA is the most common form of endocrine hypertension[1,2] and is often resistant to multiple antihypertensive drugs or their combinations.[12,13] PA is mainly caused by APA or IHA and the standard treatment is unilateral adrenalectomy for unilateral PA (APA or unilateral adrenal hyperplasia) and pharmacological therapy for bilateral PA (IHA, bilateral APA and familiar hyperaldosteronism type-1).[1,2] In this patient, unilateral APA could not be confirmed either by CT, posture stimulation test, or ACTH stimulation on dexamethasone test.[1,10,11] The PPAR γ agonist pioglitazone was added to his antihypertensive medications because PPAR γ agonists are reported to suppress aldosterone production[7] and blood pressure[8,9] and have antiproliferative and tumor-suppressive effects[5,6] and an antidiabetic effect. The addition of pioglitazone improved hypertension and hypokalemia and suppressed plasma and urinary aldosterone levels for more than 6 months. Furthermore, echocardiographic LV hypertrophy and function improved on pioglitazone