Coexistence of Renin-independent Aldosterone Secretion and Multiple Endocrine Neoplasia Type 1 Within a Family

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Abstract

Primary aldosteronism (PA) is a state of renin-independent aldosterone secretion that can range from subclinical to overt. Some normotensive individuals for whom PA screening is not routinely recommended are reported to fulfill the loading test criterion used for the diagnosis of PA. Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder characterized by the development of various endocrine tumors. Cases of PA associated with MEN1 have been reported; however, there has been no previous report on renin-independent aldosterone secretion within a family with MEN1. Herein, we present the case of a normotensive family presenting with both MEN1 and renin-independent aldosterone secretion. A 49-year-old man was admitted to our hospital for PA evaluation owing to the plasma aldosterone concentration/plasma renin activity ratio being greater than the screening cut-off value; the patient was normotensive. The patient had a history of left nephrectomy and adrenalectomy for left renal carcinoma and adrenal tumor at the age of 39 years. Subsequently, he was diagnosed with MEN1 concurrent with primary hyperparathyroidism, insulinoma, and novel MEN1 gene mutations (c.655-5_655-4insC and c.818delC). The loading tests for PA confirmation, including saline infusion, and furosemide upright and captopril challenge tests, yielded positive findings, confirming a case of renin-independent aldosterone secretion. The patient’s mother, brother, and sister were also normotensive and confirmed to have renin-independent aldosterone secretion. The coexistence of renin-independent aldosterone secretion and MEN1 within this family suggests a relationship between the 2 entities.

Key Words: renin-independent aldosterone secretion, multiple endocrine neoplasia type 1

Abbreviations: ACTH, adrenocorticotropic hormone; APA, aldosterone-producing adenoma; ARR, plasma aldosterone concentration plasma renin activity ratio; CCT, captopril challenge test; FH, familial hyperaldosteronism; FUT, furosemide upright test; MEN1, multiple endocrine neoplasia type 1; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PHPT, primary hyperparathyroidism; PRA, plasma renin activity; PTH, parathyroid hormone; SIT, saline infusion test.

Primary aldosteronism (PA) is a common cause of secondary hypertension [1], and is estimated to be observed in approximately 4% to 19% of patients with hypertension [2-4]. PA screening involves plasma aldosterone concentration (pg/mL)/plasma renin activity (ng/mL/hour) ratio (ARR) assessment; the disease is confirmed through saline infusion test (SIT), furosemide upright test (FUT), captopril challenge test (CCT), and oral salt-loading test in Japan [5]. Conventionally, PA has been screened for and diagnosed in patients with hypertension. However, emerging evidence suggests that PA may involve a continuous spectrum of renin-independent aldosterone secretion, ranging from subclinical to overt, occurring in patients with normotension and resistant hypertension, which correlates with cardiovascular disease [6-10]. Some normotensive patients for whom PA screening is not routinely recommended have high ARR values and fulfill the loading test criterion used for the diagnosis of PA [6-11]. Consequently, the prevalence of PA is likely much higher than that previously recognized. Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder caused by germline mutations of the MEN1 tumor suppressor gene [12, 13]. MEN1 is characterized by the development of primary hyperparathyroidism (PHPT), pancreatic neuroendocrine tumors, and pituitary adenomas [12, 13]. Adrenal nodules or tumors have been observed in approximately 10% to 73% of MEN1 cases [14-18]; most of them are detected as nonfunctional incidentalomas during radiological screening for MEN1. Meanwhile, approximately 15% to 20% of adrenal tumors in MEN1 are reported to have endocrine hypersecretion [17, 18]. A recent large cohort study suggested that the prevalence of PA in MEN1 patients with adrenal tumors was higher than that in patients with sporadic adrenal incidentalomas [17]. However, no previous report has evaluated renin-independent aldosterone secretion within a family with MEN1. Herein, we present the first case of a MEN1 family with normotension, in which the evaluation of renin-independent aldosterone secretion was performed.
Case Report

Plasma aldosterone concentration (PAC) was measured using radioimmunoassay (SPAC-S Aldosterone Kit; Fuji Rebio, Co., Tokyo, Japan), while plasma renin activity (PRA) was measured using enzyme immunoassay (PRA enzyme immunoassay kits; Yamasa, Co., Choshi, Japan). The reference range of PAC values measured in the supine position was from 30 to 159 pg/mL (83.2–441.1 pmol/L), and that of PRA values measured in the supine position was from 0.2 to 2.3 ng/mL/h. The intra-and interassay coefficients of variation of these PAC and PRA assay kits were reported by the manufacturer as ≤20% and ≤15%, respectively. All patients provided written informed consent for the publication of this case report, and all procedures were approved by the appropriate institutional review board (the Ethics Committee of Osaka Police Hospital) and comply with the Declaration of Helsinki and its amendments.

A man aged 49 years (patient 1) with MEN1 was referred to our hospital for PA evaluation. At the age of 39 years, the patient had undergone left nephrectomy and adrenalectomy for left renal carcinoma and adrenal tumor at another hospital. The evaluation of adrenal hormones was not performed at that time. The patient was diagnosed with PHPT at the same time and underwent parathyroidectomies of the left and right inferior glands at the age of 39 and 42 years, respectively. The pathological findings of these resected glands were consistent with parathyroid hyperplasia. At the age of 43 years, the patient was admitted to our hospital for impaired consciousness associated with hypoglycemia; at that time, he was diagnosed with multiple insulinoma, for which he underwent total pancreatectomy. At the age of 44 years, he underwent parathyroidectomy of the remaining bilateral superior glands and an autotransplantation for PHPT recurrence. Left lung lobectomy for bronchial carcinoid was also performed that same year. Genetic analysis revealed novel mutations in intron 3 (c.655-5_655-4insC) and exon 5 (c.818delC) of the MEN1 gene, resulting in the diagnosis of MEN1.

During follow-up, his family members with MEN1 were diagnosed with renin-independent aldosterone secretion, as described below. Because of the suspected association between aldosterone secretion and MEN1, the patient was screened for PA despite not developing hypertension; the patient's ARR values, measured at 2 separate assessments several months apart, were both >200, and he was not taking any medications that could affect the renin–angiotensin–aldosterone system (Table 1).

On admission, the patient's height, weight, and body mass index were 166.3 cm, 61.6 kg, and 22.3 kg/m², respectively. His blood pressure was 106/65 mmHg. He had been treated for diabetes mellitus induced by total pancreatectomy with multiple daily insulin injections. His laboratory findings are presented in Table 2. Serum potassium levels were within the normal range, PRA was undetectable (<0.2 ng/mL/hour), PAC was 191 pg/mL, and ARR was >200. Serum calcium and intact parathyroid hormone (PTH) levels were within the normal ranges, and there was no evidence of PHPT recurrence. Although the patient had a left adrenal tumor, it was resected together with his left renal carcinoma at the age of 39 years. Abdominal computed tomography scans showed no morphological abnormality of the remaining right adrenal gland. The results of loading tests used for PA diagnosis are presented in Table 1. The Japan Endocrine Society guidelines [5] state the following cut-off values as defining positive test findings: postloading PAC of >60 pg/mL (SIT), postloading PRA of <2.0 ng/mL/hour (FUT), postloading ARR of >200 (CCT). In this patient, the values of PAC after SIT, PRA after FUT, and ARR after CCT were 90 pg/mL, 0.7 ng/mL/hour, and 413, respectively. Based on positive findings from the 3 loading tests, the patient was diagnosed with renin-independent aldosterone secretion. The patient showed no evidence of chronic kidney disease, heart failure, arrhythmia, or atherosclerosis progression. He was managed with a watch-and-wait approach without pharmacotherapy, having no hypertension, hypokalemia, or signs of organ damage; the patient provided consent to this approach.

The patient's family tree and clinical characteristics are summarized in Fig. 1 and Table 3, respectively. The patient's mother (patient 2), aged 77 years, underwent parathyroidectomy of all 4 glands for PHPT at the age of 48 years; pathological findings confirmed parathyroid hyperplasia. The patient's younger brother (patient 3), aged 48 years, underwent triple parathyroidectomy for PHPT at the age of 32 years, and distal pancreatectomy for glucagonoma at the age of 43 years. Patients 2 and 3 had the same MEN1 gene mutations as did patient 1, resulting in the diagnosis of MEN1. The patient's sister (patient 4), aged 44 years, presented with PHPT and insulinoma and was also clinically diagnosed with MEN1; however, MEN1 gene analysis was not performed. All 3 family members had left adrenal tumors approximately 10 mm in diameter, and their ARR values, measured twice at different outpatient screenings, were both >200 (Table 1), without any medicines that affect the renin–angiotensin–aldosterone system; none of the patients developed hypertension. Findings from their loading tests used for PA diagnosis are presented in Table 1. SIT-positive findings confirmed renin-independent aldosterone secretion in patients 3 and 4. Patient 2 had CCT-positive findings, although both PAC and PRA levels were relatively low. In patient 2, SIT and FUT were not performed due to age; however, the rapid adrenocorticotropic hormone (ACTH) stimulation test yielded positive findings.

In all these patients, plasma cortisol concentration was suppressed to <1.8 µg/dL by 1 mg of dexamethasone, and urinary metanephrine and normetanephrine levels were within the normal range, suggesting no evidence of subclinical Cushing syndrome and pheochromocytoma. Their serum potassium levels were within the normal limit, similar to those observed in patient 1. Consequently, the patients were managed with the watch-and-wait approach without adrenal venous sampling or mineralocorticoid receptor antagonists; the patients provided their consent to this approach.

Discussion

Herein, we presented a family with clinically or genetically diagnosed MEN1 with normotension, co-occurring with renin-independent aldosterone secretion, revealed using loading test findings. To the best of our knowledge, this is the first report of concurrent MEN1 and renin-independent aldosterone secretion within a family.

Several mechanisms may explain the coexistence of these conditions. First, several studies have suggested the existence of a bidirectional interaction between aldosterone and PTH [19]. A mineralocorticoid receptor is present in the parathyroid gland, and aldosterone stimulates PTH secretion. Meanwhile, the PTH receptor is present in the adrenal gland, and PTH increases aldosterone production [20, 21].
## Table 1. Loading test results of primary aldosteronism

|                | Patient 1 |          | Patient 2 |          | Patient 3 |          | Patient 4 |          |
|----------------|-----------|----------|-----------|----------|-----------|----------|-----------|----------|
|                | PAC (pg/mL) | PRA (ng/mL/h) | ARR | PAC (pg/mL) | PRA (ng/mL/h) | ARR | PAC (pg/mL) | PRA (ng/mL/h) | ARR | PAC (pg/mL) | PRA (ng/mL/h) | ARR |
| Baseline value |           |         |           |          |           |          |           |          |           |          |           |          |          |
| First          | 178       | <0.2    | >890      | 101     | 0.4        | 253     | 138       | 0.6        | 230     | 235       | 0.6        | 392 |
| Second         | 206       | <0.2    | >1030     | 91      | 0.2        | 455     | 114       | 0.2        | 570     | 117       | 0.3        | 390 |
| SIT 0 min      | 191       | <0.2    | >955      | N/A     | N/A        | N/A     | 146       | 0.9        | 162     | 240       | 1.5        | 160 |
| SIT 240 min    | 90        | <0.2    | >450      | N/A     | N/A        | N/A     | 86        | 0.2        | 430     | 164       | 0.5        | 328 |
| FUT 0 min      | 145       | <0.2    | >725      | N/A     | N/A        | N/A     | 102       | 0.2        | 510     | 188       | 0.3        | 627 |
| FUT 120 min    | 297       | 0.7     | 424       | N/A     | N/A        | N/A     | 227       | 2.0        | 114     | 515       | 4.8        | 107 |
| FUT 60 min     | 124       | 0.3     | 413       | 59      | <0.2       | >295    | 119       | 3.5        | 34      | N/A       | N/A        | N/A |
| FUT 90 min     | 124       | 0.3     | 413       | 59      | <0.2       | >295    | 119       | 3.5        | 34      | N/A       | N/A        | N/A |
| Rapid ACTH 0 min | N/A | N/A | N/A | 42 | N/A | 7.0 | N/A | N/A | N/A | N/A | N/A |
| Rapid ACTH 30 min | N/A | N/A | N/A | 168 | N/A | 17.7 | N/A | N/A | N/A | N/A |
| Rapid ACTH 60 min | N/A | N/A | N/A | 166 | N/A | 21.0 | N/A | N/A | N/A | N/A |

Baseline values were obtained during 2 outpatient screenings performed several months apart. Test results were considered positive, given the following findings: postloading PAC of >60 pg/mL (SIT), postloading PRA of <2.0 ng/mL/h (FUT), postloading ARR of >200 (CCT), postloading peak PAC/cortisol ratio of >8.5 (rapid adrenocorticotropic hormone stimulation test). Abbreviations: SIT, saline infusion test; FUT, furosemide upright test; CCT, captopril challenge test; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, plasma aldosterone concentration/plasma renin activity ratio; cortisol, plasma cortisol concentration; N/A, not applicable.
A recent study has shown that 1% to 2% of patients with PA have PHPT [19]. In the present series, all patients had PHPT. However, given that these patients’ evaluations of renin-independent aldosterone secretion were conducted after the improvement of PTH hypersecretion by parathyroidectomies, it is unlikely that the observed renin-independent aldosterone secretion was caused by PHPT.

Second, the coexistence of renin-independent aldosterone secretion in the present MEN1 family may be explained by a gene mutation associated with familial hyperaldosteronism (FH). Although most PA cases are sporadic, approximately 1% to 5% of affected patients have familial disease forms [1, 22]. To date, 4 different forms of FH have been reported, based on the underlying genetic mutations [1, 22]. All 4 forms of FH are transmitted in an autosomal dominant pattern, and can present with a wide range of clinical and biochemical phenotypes even within the same FH family [1, 22]. In particular, FH type II has been reported as clinically and biochemically indistinguishable from the sporadic forms of PA [23]; moreover, patients with FH type I may present as normotensive [24]. Given these phenotypic characteristics of FH, the present patient family may be affected by any type of FH in combination with MEN1. However, the probability that 2 rare hereditary diseases overlap in 1 family is extremely low.

Another possible cause of concurrent renin-independent aldosterone secretion and MEN1 within a family may be a direct interaction between MEN1 gene mutation and aldosterone hypersecretion. To date, numerous germline mutations in the MEN1 gene have been reported; they tend to be distributed throughout the coding region without any significant hotspots [25, 26]. MEN1 gene analysis in the present

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**Table 2.** Laboratory findings of patient 1 at the time of admission

| Blood test findings | Value          | Reference Range          |
|---------------------|----------------|--------------------------|
| WBC                 | 5100/µL (3500-9800) | Na 140 mEq/L (135-147)   |
| RBC                 | 395 x 10⁶/µL (427-570) | K 4.3 mEq/L (3.6-5.0)    |
| Hb                  | 12.1 g/dL (13.5-17.6) | Cl 102 mEq/L (98-108)     |
| Plt                 | 35.9 x 10⁹/µL (13.1-36.2) | Ca 8.2 mg/dL (8.8-10.2)  |
|                     |                | P 3.9 mg/dL (2.3-5.0)    |
| Biochemistry findings |                  | FPG 193 mg/dL (70-110)   |
| TP                  | 6.2 g/dL (6.7-8.2) | HbA1c 7.5% (4.6-6.2)     |
| Alb                 | 3.2 g/dL (4.0-4.8) | AST 29 U/L (10-33)       |
| T-cho               | 182 mg/dL (139-220) | ALT 21 U/L (6-35)        |
| TG                  | 73 mg/dL (36-149) | ALP 241 U/L (120-340)    |
| HDL-C               | 54 mg/dL (40-87) | iPTH 18 pg/mL (10-65)    |
| LDL-C               | 105 mg/dL (69-139) | ACTH 51.5 pg/mL (7.2-63.3) |
| UN                  | 15.8 mg/dL (8.4-20.4) | Cortisol 17.7 µg/dL (3.7-19.4) |
| Cr                  | 0.88 mg/dL (0.62-1.04) | DHEA-S 89 µg/dL (123-422) |
| eGFR                | 73.5 mL/min/1.73 m² | PAC 191 pg/mL (30-159)   |
| UA                  | 4.1 mg/dL (2.2-6.7) | PRA <0.2 ng/mL/h (0.2-2.3) |

Reference ranges are in parentheses.

Abbreviations: Alb, albumin; ACTH, adrenocorticotropic hormone; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ca, calcium; Cl, chloride; Cr, creatinine; DHEA-S, dehydroepiandrosterone-sulfate; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; Hb, hemoglobin; Hba1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; iPTH, intact parathyroid hormone; K, potassium; LDL-C, low-density lipoprotein cholesterol; Na, sodium; P, phosphorus; PAC, plasma aldosterone concentration; Plt, platelet count; PRA, plasma renin activity; RBC, red blood cell count; T-Cholesterol; TG, triglyceride; TP, total protein; UA, uric acid; UN, blood urea nitrogen; WBC, white blood cell count.

**Figure 1.** Family tree of the patients reported in this case series. Filled circles or squares indicate affected individuals.
In general, patients with APA have high levels of aldosterone-producing adenoma (APA) and idiopathic hyperaldosteronism. Further studies of this presentation; thus, any conclusions regarding this association should be considered preliminary. Further studies have examined the association between genotype and renin-independent aldosterone secretion. However, few previous studies have explored the association between genotype and occurrence of adrenal lesions or hormonal hypersecretion, and the prevalence of PA in patients with MEN1 cases without adrenal tumors. Adrenal tumors are identified in fewer than half of PA cases; meanwhile, idiopathic hyperaldosteronism accounts for over 70% of cases [4, 30]. Given the present case findings and evidence overall, we speculate that the evaluation of renin-independent aldosterone secretion in patients with MEN1, particularly those with its mild form that involves normotension and normokalemia, may have been insufficient, resulting in an underestimated prevalence. To clarify the relationship between renin-independent aldosterone secretion and MEN1, large cohort studies of patients with or without adrenal tumors and involving molecular analyses are required.

In the present family, none of the patients developed hypertension. If aldosterone secretion in the present patients was caused by a germline mutation such as in FH-related genes or the MEN1 gene, the patients would have likely developed early onset hypertension. However, hypertension is not always observed early even if it is caused by a germline mutation, as it depends on the severity of aldosterone secretion, vascular compliance capacity to handle the excess volume, and/or nephron capacity to excrete the excess sodium/volume [9, 10]. In fact, FH does not always translate to early onset hypertension [31]. Of note, normotensive patients with renin-independent aldosterone secretion are at a higher risk of developing hypertension than those without renin-independent aldosterone secretion [8-11]. In addition, if hypertension develops, treatment with mineralocorticoid receptor antagonists may be more useful than that with other antihypertensive medications; thus, the patients in this case series should be closely monitored for signs of hypertension. Furthermore, owing to the possible association between renin-independent aldosterone secretion and MEN1, screening for PA status in other MEN1 patients, at least those with hypertension, may be considered.

A growing body of evidence suggests that patients with PA have a higher risk of cardiocerebrovascular disease, heart failure, chronic kidney disease, and metabolic disease than do those with essential hypertension [32]. Surgical adrenalectomy for unilateral APAs can improve hypertension

**Table 3.** The patients’ demographic and clinical characteristics.

| Patient | Sex | Age (years) | MEN1 gene mutation | PHPT | NET | Pituitary adenoma | Adrenal lesion | Renin-independent aldosterone secretion | SIT | FUT | CCT | Rapid ACTH |
|---------|-----|------------|---------------------|------|-----|------------------|---------------|------------------------------------|-----|-----|-----|------------|
| 1       | Male| 49         | +                   | +    | Insulinoma | –                | Left (postoperation) (11 mm) | +                   | N/A | –   | +   | N/A        |
| 2       | Female| 77        | +                   | +    | –           | Glucagonoma       | Left (8 mm)     | +                   | N/A | N/A | +   | N/A        |
| 3       | Male| 48         | +                   | +    | –           | –                | Left (10 mm)    | +                   | N/A | –   | –   | –          |
| 4       | Female| 44        | +                   | +    | –           | –                | –              | +                   | N/A | –   | –   | –          |

Abbreviations: PHPT, primary hyperparathyroidism; NET, neuroendocrine tumor; SIT, saline infusion test; FUT, furosemide upright test; CCT, captopril challenge test; N/A, not applicable.
and aldosterone excess [1]. Treatment with mineralocorticoid receptor antagonists may help reduce the risk of organ damage [33]. In contrast, the evidence showing treatment efficacy in normotensive patients with renin-independent aldosterone secretion is insufficient, and further studies are needed in this regard. In the present family, patients were managed with a watch-and-wait approach rather than pharmacotherapy due to normotension, normokalemia, and no evidence of organ damage. However, normotensive patients with renin-independent aldosterone secretion may have greater mineralocorticoid receptor activity than those without renin-independent aldosterone secretion [6]. Consequently, these patients should be monitored for any signs of organ damage.

This case series has several limitations. First, we could not evaluate the PA status in the remaining family members without MEN1 because of their lack of consent. The absence of evidence indicative of renin-independent aldosterone secretion in the remaining family members may suggest a link between MEN1 and renin-independent aldosterone secretion. Although approximately 6% to 14% of patients with normotension have been reported to have renin-independent aldosterone secretion [6-11], all 4 members diagnosed with MEN1 in the present family had renin-independent aldosterone secretion. This makes an incidental accumulation of these cases unlikely and suggests a connection between MEN1 and renin-independent aldosterone secretion. Second, patient 2 had increased ARR and CCT-positive findings, and relatively low values of both PAC and PRA, which may have yielded false-positive results. However, findings from a rapid ACTH stimulation test to confirm aldosterone overproduction by ACTH were positive. Meanwhile SIT and FUT could not be performed owing to the advanced age of patient 2. In the rapid ACTH stimulation test, peak PAC/plasma cortisol concentration ratio >8.5 after stimulation is defined as a positive finding [34]. Although not included in the current guidelines, it has been suggested as useful for the diagnosis of PA [34]. Thus, patient 2 may have had mild renin-independent aldosterone secretion. Third, as we did not perform adrenal venous sampling, the source of aldosterone production was unknown. In addition, we could not confirm aldosterone hypersecretion using pathological findings, including immunohistochemical staining of CYP11B2 in any of the cases owing to ethical constraints. However, accumulating evidence on the spectrum of renin-independent aldosterone secretion, assessed mostly with biochemical tests, and positive findings from loading tests in this family suggest that the patients in this case series had mild renin-independent aldosterone secretion, although their phenotypes were inconsistent with those of classical overt PA. Finally, genetic analyses of FH types were not performed. However, the probability that 2 rare hereditary diseases, MEN1 and FH, overlap in 1 family is extremely low. Despite these limitations, the present case series may contribute insights into the relationship between renin-independent aldosterone secretion and MEN1.

The present cases series is the first to report on a family with coexistence of MEN1 with normotension and renin-independent aldosterone secretion, revealed using loading tests for PA diagnosis. Large cohort studies and molecular investigations are required to clarify the relationship between renin-independent aldosterone secretion and MEN1.

Disclosures
The authors declare no conflict of interest associated with this manuscript.

Data Availability
Data sharing is not applicable to this article because no data sets were generated or analyzed during the present study.

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