A case of ACTH-independent macronodular adrenal hyperplasia associated with multiple endocrine neoplasia type 1

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Abstract. Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant neoplasia syndrome characterized by the occurrence of tumors in the parathyroid glands, pancreas, and anterior pituitary. Approximately 30–40% of MEN1 patients also have adrenal lesions, such as hyperplasia, benign adenoma, and adrenocortical carcinoma. Most of the cases are hormonally silent. We describe the case of a 60-year-old man with bilateral macronodular adrenal lesions, in addition to parathyroid tumors, multiple insulinomas, and non-functioning pituitary microadenoma. Endocrinological tests revealed subclinical hypercortisolism; midnight cortisol level rose slightly (8.0 µg/dL), although basal plasma ACTH and cortisol levels were within the normal range (19.5 pg/mL and 12.0 µg/dL, respectively). One and 8 mg dexamethasone suppression tests showed cortisol levels of 2.3 and 9.8 µg/dL, respectively. 131I-adosterol scintigraphy under dexamethasone suppression revealed bilateral adrenal uptake with right-sided predominance. The histological features of the removed right adrenal gland were consistent with ACTH-independent macronodular adrenal hyperplasia (AIMAH): immunoreactivity of 17α-hydroxylase was predominantly observed in the small compact cells, while that of 3β-hydroxysteroid dehydrogenase was exclusively expressed in the large clear cells. The glucose-dependent insulinotropic polypeptide (GIP) receptor was expressed at high levels in compact cells, suggesting that GIP is responsible for the development of AIMAH. Unilateral small adrenal lesions were detected in the patient’s 2 children, who also presented with MEN1 symptoms. Genetic abnormalities in the MEN1, p27, and p18 genes were not found, however, the present case may provide a clue to the understanding of the etiology of MEN1 and AIMAH.

Key words: AIMAH, Cushing syndrome, MEN type 1, MEN1 gene, GIP

ACTH-INDEPENDENT macronodular adrenal hyperplasia (AIMAH) is a unique and rare disorder which is characterized by bilateral massive enlargement with autonomous cortisol production [1, 2]. AIMAH accounts for less than 1% of ACTH-independent Cushing syndrome (CS), and the extent of cortisol excess ranges from subclinical to overt CS level. The vast majority of patients with AIMAH are sporadic, but a few familial cases have been reported [3-6]. The latter cases exhibit an autosomal dominant inheritance; however, their genetic defect has not been identified yet.

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant neoplasia syndrome that affect the parathyroid glands, pancreas, anterior pituitary, and other endocrine organs [7]. The most common manifestation of MEN1 is hyperparathyroidism, but adrenal lesions are also observed in approximately 30–40% of MEN1 patients [8-13]. In MEN1 patients with adrenal involvement, there is a broad range of histological features, including uni- or bilateral hyperplasia, benign adenoma, and less frequently, adrenocortical carcinoma; however, most of such cases
are non-functional. On the other hand, “functional” bilateral nodular hyperplasia is rarely seen in MEN1 patients. In the present study, we describe a MEN1 patient with AIMAH confirmed by hormonal and histological examination. In addition, the change in size and function of the remaining left adrenal gland were regularly followed after unilateral adrenalectomy, and the adrenal lesions of his 2 children presenting with MEN1 symptoms were also evaluated.

**Materials and Methods**

**Biochemical assays**

Blood samples were obtained on the morning after an overnight fast and a 30-min resting period in the supine position. Hormones were measured by commercial RIA or enzymatic immunoassay (EIA) kits. For low or high dose dexamethasone suppression test (DST), 1 or 8 mg of dexamethasone was administered at 2300 h, respectively. ACTH and cortisol values were measured the next morning.

**Histology**

Tissue samples obtained during surgery were fixed in 10% formalin solution and embedded in paraffin. Sections were stained with hematoxylin-eosin (HE). Immunohistochemical staining of 17α-hydroxylase (P-450\_17α), 3β-hydroxysteroid dehydrogenase (3βHSD), and insulin were performed with formalin-fixed, paraffin-embedded sections using the biotin-streptavidin amplified method and Histofine immunostaining system (Nichirei Co. Ltd., Tokyo, Japan). The procedures and primary antibodies used in this study have been described previously [14]. Phosphate buffered saline (0.01 mol/L) and normal rabbit IgG were used as negative controls. Immunohistochemical analysis of the glucose-dependent insulinotropic polypeptide receptor (GIPR) was performed using a polyclonal antibody to GIPR (LS-A3840, Lifespan Bioscience, Seattle, WA). Sections were deparaffinized with xylene and microwave (500 W) for 15 minutes in citric acid buffer (2 mmol/L citric acid and 9 mmol/L trisodium citrate dehydrate, pH 6.0) for antigen retrieval. The primary antibody was diluted 1:200. Reactivity was detected through a system of peroxidase-conjugated polymers (EnVision/HRP system, K1491, DAKO, Tokyo, Japan).

**Preparation of DNA and sequence analysis**

DNA was extracted from peripheral blood leukocytes using standard methods. The direct DNA sequencing reaction of all PCR-amplified exons and splice junctions of **MEN1** gene of the proband was performed by Noguchi Hospital (Beppu, Japan)[15] and FALCO biosystems (Kyoto, Japan). Southern blotting analysis using exon 2 and exon 10 probes was performed by Mitsubishi Chemical Medience Corporation (Tokyo, Japan). Multiplex ligation-dependent probe amplification (MLPA) analysis was performed by FALCO biosystems; the presence of a large deletion was evaluated by the relative copy number ratios between the peak height value of each PCR sample and the normal control, calculated using the Salsa MLPA kit (MRC-Holland, Amsterdam, the Netherlands). In addition, all coding regions and exon-intron boundaries of the **p27** and **p18** genes were sequenced. Permission for these genetic studies was obtained from the patient and the ethical committee of Nagoya University School of Medicine.

**Case Report**

A 60-year-old man was referred to Nagoya Ekisaikai Hospital for further examination of neck swelling in the year 2000. He had been followed up by a general physician because of hypertension and hyperlipidemia. He had been suffering from colic pain due to ureteral stones since his forties and receiving extracorporeal shock wave lithotripsy. Blood examination revealed hypercalcemia (12.1 mg/dL) and hypophosphatemia (2.0 mg/dL) with a high level of plasma intact PTH (700 pg/mL). A neck computed tomography (CT) scan showed large bilateral tumors in the extrathyroidal region, indicating primary hyperparathyroidism. He was referred to the Department of Breast and Endocrine Surgery of Nagoya University Hospital and underwent a parathyroidectomy. The sizes of 3 removed tumors were 52×39 mm (right, upper), 25×21 mm (left, upper), and 20×12 mm (left, lower) in diameter (Fig. 1A). Serum calcium level was normalized after surgery. In addition, abdominal CT scan revealed multiple pancreatic tumors (Fig. 1B) and a striking bilateral macronodular adrenal lesion (Fig. 1C, D). Arterial stimulation and venous sampling showed that immunoreactive insulin (IRI) was markedly elevated from 150 to 3969 µU/mL after bolus calcium infusion was administered into the splenic artery, indicating the presence of insulin-secreting tumors. In addition, magnetic resonance imaging (MRI) showed a 4-mm...
AIMAH associated with MEN type 1

The circadian regulation of the hypothalamo-pituitary-adrenal (HPA) axis. High dose dexamethasone failed to suppress cortisol. 131I-adosterol scintigraphy was performed under the administration of 2 mg per day of dexamethasone and showed that the adrenal uptake was marked in the right adrenal gland and faint in the left (Fig. 1F). To suppress ACTH secretion completely, dexamethasone was administered from 2 days before the radionuclide injection to the end of image acquisition. This asymmetric uptake suggests that the extent of autonomous cortisol production of the right adrenal gland was predominant. The hormonal and radiological examination fulfilled the diagnostic criteria of subclinical CS (SCS).

The 75 g oral glucose tolerance test (OGTT) showed a diabetic pattern (Table 1C). The patient had diabetes despite the presence of insulinoma, probably because of the circadian regulation of the hypothalamo-pituitary-adrenal (HPA) axis. High dose dexamethasone failed to suppress cortisol. 131I-adosterol scintigraphy was performed under the administration of 2 mg per day of dexamethasone and showed that the adrenal uptake was marked in the right adrenal gland and faint in the left (Fig. 1F). To suppress ACTH secretion completely, dexamethasone was administered from 2 days before the radionuclide injection to the end of image acquisition. This asymmetric uptake suggests that the extent of autonomous cortisol production of the right adrenal gland was predominant. The hormonal and radiological examination fulfilled the diagnostic criteria of subclinical CS (SCS).

The patient was admitted to Nagoya University Hospital for further examination of proteinuria in 2002. He was 172 cm tall and weighed 79 kg. He had no Cushingoid features. His blood pressure was 154/94 mmHg. Interestingly, sulfonylurea (glyclazide 40 mg/day) administration had been started by another hospital, because HbA1c level was elevated to 8.5%. He had preproliferative diabetic retinopathy and early diabetic nephropathy with nephrosclerosis, as confirmed by renal biopsy. Caloric restriction for his diabetes was performed during hospitalization; subsequently, he had occasional hypoglycemic attacks. Fasting plasma glucose (PG) was 26 mg/dL with elevated C-peptide (6.38 ng/mL) even after glyclazide was discontinued. Results of the blood examination are shown in Table 1. The rise of midnight cortisol suggests the disturbance of non-functioning pituitary microadenoma (Fig. 1E).

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![Fig. 1](image-url)

MEN1 symptoms of the proband. A, Macroscopic findings of the 3 removed parathyroid glands. B–D, Serial dynamic abdominal CT imaging. Hypervascular tumors were detected in pancreas (B). Bilateral adrenal macronodular lesions were observed in the lower slices (C and D). E, Enhanced MRI imaging of pituitary. A low-intensity mass was found at the left side of pituitary on a T1-weighted image. F, Adrenal scintigraphy. Image obtained at 9 days after the injection of beta-131I-iodomethylnorcholesterol is presented. Dexamethasone was administrated constantly during the examination. A marked adrenal uptake was observed in the right adrenal gland, unlike that in the left.
enlarged, measuring 40×35×50 mm and weighing 36 g. The cut surface was yellowish and displayed multiple nodules (Fig. 2A). Microscopically, these nodules were composed of 2 distinct types of cells: large clear cells forming cordon nest-like structures, and smaller compact cells forming island-like structures (Fig. 2B). The normal architecture of the internodular adrenal cortex was not observed. Immunoreactivity of P-450\textsubscript{17α} was seen predominantly in the compact cells (Fig. 2C, D), while that of 3βHSD was observed exclusively in the clear cells (Fig. 2E, F).

Hypercortisolism causes strong insulin resistance. Diabetic retinopathy and nephropathy were unexpectedly advanced, suggesting a long history of diabetes. Hypoglycemia due to the insulinomas may prevent HbA1c from rising over a long period of time. The diabetic complications may have worsened during that period. In addition, the repeated hypoglycemic attacks may have accelerated the retinopathy [16].

Later in 2002, a spleen-preserving distal pancreatectomy and a right adrenalectomy were carried out. The removed adrenal gland was extremely enlarged, measuring 40×35×50 mm and weighing 36 g. The cut surface was multinodular and bright yellow. The nodules were composed of large clear cells and smaller compact cells. The diabetic complications may have worsened during that period. In addition, the repeated hypoglycemic attacks may have accelerated the retinopathy [16].

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AIMAH associated with MEN type 1 tumorigenesis [18, 19].

The patient’s 33-year-old son and 38-year-old daughter also presented with the typical symptoms of MEN1. A family tree and the clinical manifestations of the affected members are shown in Fig. 5. The patient’s son (III-3) underwent a distal pancreatectomy because of insulinoma and total parathyroidectomy with subsequent autologous transplantation at the ages of 15 and 30, respectively. Pituitary MRI revealed 2 non-functioning microadenomas (less than 5 mm in size). Interestingly, a small nodular lesion was observed in the left adrenal gland (Fig. 6A, B), while the size of the right gland was equivocal. His basal ACTH level was 30.1 pg/mL (cortisol was not examined). Morning plasma cortisol level decreased to 0.7 µg/dL, and ACTH was undetectable in the 1 mg DST, indicating that his adrenal lesion was non-functioning.

The daughter (III-1) underwent a parathyroidectomy at the age of 34. Two years later, she underwent distal pancreatectomy and partial hepatectomy because of pancreatic and liver tumors. Gastrin, but not insulin, was positive in the resected multiple pancreatic tumors. A few glucagon and somatostatin immunoreactive cells were observed. On the other hand, the pathological finding of the liver mass revealed peliosis hepatis, which is a rare manifestation of MEN1. She also had pituitary prolactinoma, and the serum prolactin level was normalized with cabergoline treatment. Her left pattern of these steroidogenic enzymes was consistent with the histological features of AIMAH [14]. On the other hand, 6 pathologically confirmed insulinomas were found in the resected pancreas (Fig. 2G, H).

The remaining left adrenal gland had already been enlarging for 4 years, and more significantly, for 7 years after surgery (Fig. 3A, B). Morning plasma ACTH and cortisol levels were 22.8 pg/mL and 10.6 µg/dL, respectively. One and 8 mg DST showed morning cortisol levels of 1.8 and 1.7 µg/dL, respectively, indicating that autonomous cortisol production was improved after right adrenalectomy. The pituitary microadenoma was not enlarged. Abdominal CT revealed that the tumor had recurred (15 mm in size) in the head of the pancreas. This tumor was not removed because there was no hypoglycemic attack.

Cortisol secretion in AIMAH is mediated by the aberrant expression of membrane receptors for vasopressin, GIP, catecholamine, serotonin, and LH/hCG [1, 2]. Chronic stimulation of these G protein-coupled receptors (GPCRs) by their respective ligands plays an important role in AIMAH development. Interestingly, immunoreactivity of GIPR was detected abundantly in compact cells and sparsely in clear cells (Fig. 4A–D). This observation suggests that the aberrant GIPR expression is involved in the progression of AIMAH.

Sequencing analysis of all of the coding regions of the MEN1 gene from peripheral blood failed to show any mutation. A large germline deletion spanning the whole MEN1 gene was examined by Southern blotting analysis using exon 2 and exon 10 probes, but no abnormality was detected. A large deletion of 1 or more exons of the MEN1 gene was undetectable in MLPA analysis [17]. In addition, mutations were not found in the coding regions of 2 cyclin-dependent kinase inhibitor (CDKI) genes, p27 (CDKN1B) and p18 (CDKN1C), which have been implicated in MEN1 tumorigenesis [18, 19].

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patients had bilateral macronodular adrenal hyperplasia, which was composed of uniform clear cells resembling zona fasciculata cells [9]. However, 1 was hormonally silent, and the other was not examined for cortisol levels. In a more recent study, among 18 MEN1 patients with adrenal lesions, the histological examination of 2 patients revealed macronodular hyperplasia of the adrenal cortex with bilateral adrenal CS [10].

Fig. 5 Pedigree diagram of the proband’s family. Family members are indicated by generations (Roman numbers) and individuals (Arabic numbers) Circles, females; squares, males; arrow, proband. Empty and filled symbols indicate unaffected and affected family members, respectively.

Adrenal abnormality is often recognized in MEN1 patients, but it encompasses solitary adenoma, hyperplasia, and carcinoma. The verification of autonomous cortisol secretion is needed to confirm the diagnosis of AIMAH; however, in the previous 6 studies of MEN1 patients with adrenal lesions (total 120 cases), functional bilateral hyperplasia was rare [8-13]. Skogseid et al. reported that adrenal involvement was observed in 11 of 33 MEN1 patients and that 7 had bilateral enlargement [8]. There was no evidence of cortisol hypersecretion, because the results of diurnal cortisol variation and DST were normal in all subjects. According to another study on 33 patients from a single and large kindred of MEN1 (known as Tasman1), 2

Discussion

In this paper, we describe a patient with AIMAH who also presented with typical MEN1 symptoms. He had hyperparathyroidism due to multiple parathyroid tumors, multiple insulin-secreting tumors in the pancreas, and a non-functioning pituitary tumor. The adrenal lesions of his 2 children having MEN1 manifestations were also evaluated.

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Fig. 6 Adrenal lesions of the 2 children of the proband. A and B, Adrenal lesion of son. A small nodular lesion was observed in the left adrenal gland, while the size of the right gland was equivocal. C and D, Adrenal lesion of daughter. Thickening of the left adrenal gland was observed.
together, bilateral adrenal involvement is often observed in MEN1 patients; however, there are probably very few cases corresponding to AIMAH, based on clinical and histological evidence. On the other hand, it is undeniable that the occurrence of AIMAH is underestimated when patients present with SCS.

The pathological findings of AIMAH are characteristic: nodules consist of 3βHSD-positive clear cells and P-45017α-positive smaller compact cells [14]. The differential distribution pattern of the steroidogenic enzymes is assumed to cause the low efficacy of cortisol production in the large-sized adrenals of patients with AIMAH. In addition, this immunohistological feature is observed only in AIMAH and not in other adrenal diseases. For example, in the cases of MEN1 patients with ACTH-producing pituitary tumor, the chronic ACTH stimuli cause the bilateral adrenal hyperplasia; however, its histological changes differ from those of AIMAH [1, 2, 20]. In the present case, the histological features were compatible with AIMAH.

In spite of many clinical and molecular investigations, the etiology of AIMAH has not been fully elucidated yet. To date, the pathogenesis of AIMAH is thought to be substantially heterogeneous [1, 21, 22]. Clonal analysis shows the existence of a polyclonal pattern between nodules in the same AIMAH patient [21]. On the other hand, it is assumed that the abnormality of the intracellular cAMP/protein kinase A (PKA) signaling pathway plays an important role in AIMAH genesis [1]. Moreover, recent studies show that long-term stimulation by various kinds of ligands for aberrant receptors expressed in adrenals, such as vasopressin, GIP, and β-adrenergic agonist, are involved in the formation of this unique adrenal lesion [1, 2]. GIPR is expressed in normal β cells and insulinoma cells but not in normal adrenocortical cells [23]. In the present case, immunohistochemical studies revealed abundant expression of GIPR. Our results suggest that this adrenal lesion was GIP-dependent AIMAH, although glucose- or food-dependent increases in cortisol levels were not confirmed before surgery. The ectopic expression of GIPR was probably responsible for AIMAH development, and this mechanism could also account for the enlargement of the left adrenal lesion after surgery. Notably, GIPR expression was intense in compact cells and sparse in clear cells. This differential distribution pattern, which is similar to that of steroidogenic enzymes, may have some effects on the efficacy of cortisol production and/or secretion.

The incidence of food- or GIP-dependent AIMAH is comparatively rare and has not been reported in familial cases of AIMAH [4-6]. In a microarray study of several types of AIMAH, analysis of gene expression profiles by hierarchical clustering revealed a distinct gene expression pattern in GIP-dependent AIMAH, which was different from that of non-GIP AIMAH [22]. This observation suggests that GIP-dependent AIMAH is fundamentally different from non-GIP AIMAH.

Before surgery, cortisol level in the 8 mg DST was higher than that in the 1 mg DST (Table 1). According to the Japanese diagnostic criteria for SCS [24], the former was positive (>1 µg/dL) and the latter was negative (<3 µg/dL). A similar discrepancy is often seen in SCS patients [25]. Interestingly, urinary free cortisol levels paradoxically increase in response to dexamethasone treatment in a dose-dependent manner in some (4 of 9) patients with AIMAH [26]. This paradoxical response to dexamethasone is also observed in most patients with primary pigmented nodular adrenocortical disease (PPNAD). Therefore, the glucocorticoid-dependent increase in cortisol levels was not specific to the present case. The 1 mg and 8 mg DSTs performed after surgery did not reveal this response, suggesting that the adrenals have a significant laterality in their responsiveness to exogenous glucocorticoids as well as steroidogenic efficacy.

A genetic defect in the MEN1 gene is responsible for MEN1, whereas approximately 10–30% of MEN1 patients do not have this gene mutation [7, 18, 19]. The MEN1 gene contains 10 exons (the first of which is untranslated) that extend over 9 kbp of chromosome 11q13. Gross deletions in the MEN1 gene are found in a few cases of MEN1 patients who are negative for mutations on routine direct sequence [17]. In our case, the presence of a gross deletion was not recognized by MLPA analysis. On the other hand, CDKI family members, which regulate the cell cycle progression, were recently identified as MEN1-causing genes [18, 19, 27]; several heterozygous p27 (CDKN1B) gene mutations have been detected in MEN1 or MEN1-like patients. Among 196 MEN1 patients with no genetic alterations in the MEN1 gene, 3 patients had a mutation in p27, and 4 had mutations in other CDKI genes (p18, p15, and p21) [19]. We therefore sequenced all the coding regions of the p27 and p18 genes, but failed to detect any mutation. Our patient and his children presented with apparent MEN1 symptoms, but the causative gene could not be identified.
Another clue to solve this problem was the fact that pancreatic endocrine tumors were present in all the MEN1 patients with adrenal lesions [8, 9]. This finding suggests a close relationship between the endocrine pancreas and the adrenal lesion. This patient had multiple insulinomas in the pancreas as well. However, Barzon et al. show that no apparent adrenal lesion is observed in patients with isolated pancreatic endocrine tumors, which are unrelated to MEN1 [13]. Thus, the hypersecretion of pancreatic hormones or growth factors alone is not the cause of the initiation of the adrenal neoplastic process. In the presence of a genetic defect, the endocrine pancreas may affect the development of AIMAH directly or indirectly. On the other hand, some of the hormones induced by repeated hypoglycemia, such as ACTH and catecholamine, may predispose to nodular cell proliferation. However, this possibility is low, considering the relatively rapid growth of the left adrenal gland after the removal of the insulinomas. Adrenal enlargement was also observed in the patient’s 2 children in their thirties, who presented with pancreatic endocrine tumors. Their adrenal lesions may stay constant or more likely, progress to AIMAH in the future, because asymmetric development of adrenals is often observed in AIMAH patients. A careful, long-term follow-up is necessary to monitor the adrenal lesion of these patients.

The present study describes the case of a MEN1 patient with AIMAH, which was confirmed by hormonal and histological examination. Immunohistochemical analysis suggests that this adrenal lesion was GIP-dependent AIMAH. Our case may provide insight into the etiology of MEN1 and AIMAH.

References


