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【 CASE REPORT 】

Multiple Endocrine Neoplasia Type 1 with Functional Parathyroid Cysts

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Abstract:
A 51-year-old woman was admitted because of hypercalcemia. Neck ultrasonography and computed tomography revealed the presence of parathyroid cysts on both sides. After primary hyperparathyroidism was diagnosed by technetium-99m-methoxyisobutylisonitrile scintigraphy, the patient was successfully treated with total parathyroidectomy and autotransplantation. She also had a non-functioning pancreatic neuroendocrine tumor, prolactinoma, and adrenal tumors with subclinical Cushing's syndrome. Given these clinical features and her family history, multiple endocrine neoplasia type 1 (MEN1) was suspected, and germline DNA sequencing revealed a missense mutation (c.1013T>G, p.Leu338Pro) in exon 7 of *MEN1*. This case demonstrates the phenotypic and genetic diversity of MEN1.

Key words: *MEN1* mutation, family history, functional parathyroid cysts, pancreatic neuroendocrine tumor, prolactinoma, subclinical Cushing's syndrome

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Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disease with a low prevalence of approximately 1 per 100,000 individuals (1). This syndrome is characterized by functioning or non-functioning tumors occurring in multiple endocrine organs that classically involve ≥2 parathyroid glands (>95% penetrance), the endocrine pancreas (>50% penetrance), and pituitary gland (20-30% penetrance) (2, 3). The clinical manifestations depend on the tumor site and the presence or absence of hormone-producing functions. As the parathyroid glands are the most frequently affected organ in MEN1, the clinical phenotype of MEN1 is represented by hypercalcemia and its associated diseases due to primary hyperparathyroidism, such as urolithiasis, gastroduodenal ulcer, and arrhythmia. Primary hyperparathyroidism in MEN1 is pathologically characterized by multinodular hyperplasia of the parathyroid glands, whereas adenomas, carcinomas, and cystic lesions in sporadic primary hyperparathyroidism have rarely been reported in MEN1 (4).

MEN1 is caused by germline mutations in the tumor suppressor gene *MEN1*, which is localized on chromosome 11 (11q13) and encodes the protein MENIN (5). Approximately 1,700 mutations with high penetrance are broadly distributed in the *MEN1* gene, and clustering of mutations is observed in exons 2 and 10 (6, 7). However, previous studies have not established clear genotype-phenotype correlations of *MEN1* mutations (6). Germline mutational testing for the *MEN1* gene is recommended for patients presenting with these clinical and pathological characteristics and first-degree relatives (3).

We herein report a case of familial MEN1 with parathyroid cysts and a germline missense mutation in the *MEN1*

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Table 1. Laboratory and Basal Endocrinological Findings.

Parameter	Values	Reference range
Serum albumin, g/dL	3.9	3.8-5.3
Serum calcium, mg/dL	13.6	8.4-10.2
Serum phosphate, mg/dL	2.2	2.5-4.5
Alkaline phosphatase, U/L	618	104-338
Intact PTH, pg/mL	498	10-65
PTH-rP, pmol/L	<1.1	<1.1
1,25-dihydroxyvitamin D, pg/mL	116	20-60
Urine calcium, mg/dL	12.0	NA
Urine phosphate, mg/dL	95.8	NA
Serum cleatinine, mg/dL	0.71	0.40-0.80
eGFR, mL/min/1.73m2	67.5	90-120
HbA1c, %	5.8	4.3-5.8
Fasting serum glucose, mg/dL	172	70-110
ACTH, pg/mL	14	7-56
Cortisol, μg/dL	11.5	4.0-19.3
TSH, μU/mL	3.52	0.49-4.67
Free T3, pg/mL	2.43	1.45-3.48
Free T4, ng/dL	1.20	0.71-1.85
Prolactin, ng/mL	57.23	6.12-30.54
LH, mIU/mL	21.50	5.72-64.31
FSH, mIU/mL	61.80	<157.79
Estradiol, pg/mL	<10	<18
Growth hormone, ng/mL	0.023	0.010-3.607
IGF-1, ng/mL	173	79-215
Gastrin, pg/mL	461	37-172
Insulin, μU/mL	14.3	2-12
Glucagon, pg/mL	192	23-197
VIP, pg/mL	91	<100
PRA, ng/mL/h	5.9	0.2-2.7
PAC, pg/mL	355	30-159
DHEA-S, μg/dL	15	18-210
Urine metanephrine, mg/gCr	0.16	NA
Urine normetanephrine, mg/gCr	0.16	NA
Urine 5-HIAA, mg/day	1.7	0.6-4.1

ACTH: adrenocorticotropic hormone, TSH: thyroid-stimulating hormone, T3: triiodothyronine, T4: thyroxine, LH: luteinizing hormone, FSH: follicle-stimulating hormone, IGF-1: insulin-like growth factor-1, VIP: vasoactive intestinal peptide, PRA: plasma renin activity, pAC: plasma aldosterone concentration, DHEA-S: dehyroepiandrosterone sulfate, HIAA: hydroxyindole acetic acid, NA: not available

gene. This unusual case of MEN1 shows phenotypic and genetic diversity of this disorder, since only five MEN1 patients with parathyroid cysts have been reported to date.

Case Report

A 51-year-old woman was referred and admitted to the hospital because of hypercalcemia and high serum gastrin levels. She experienced fatigue, epigastralgia, and appetite loss that continued for one month. Upper gastrointestinal endoscopy revealed reflux esophagitis and duodenal ulcer. She had a history of being treated for urethral stones at 34 and 45 years old.

The patient's laboratory and basal endocrinological findings on admission are presented in Table 1. Her serum calcium level was 13.7 mg/dL, serum phosphate level was 2.3 mg/dL, and serum intact parathyroid hormone (PTH) level was 498 pg/mL (normal range: 10-65 pg/mL). Her PTH-related protein level was less than 1.1 pmol/L (normal range: less than 1.1 pmol/L). Ultrasonography and computed tomography (CT) of the neck showed a cystic mass with a hypervascular solid lesion located on each side of the inferior portion of the thyroid gland (Fig. 1). Both masses had high uptakes on technetium-99 m-methoxyisobutylisonitrile (MIBI) scintigraphy (Fig. 2), showing that these cystic masses functioned as parathyroid glands. Thus, the patient was diagnosed with primary hyperparathyroidism based on these results. The bone mineral density and T-score of the patient's lumbar spine (2nd-4th lumbar vertebra) on dual X-ray absorptiometry were 0.726 g/cm^2 and -2.57, respectively, corresponding to 72% of the young adult mean values. In addition, her serum gastrin level was 461 pg/mL (normal range: 37-172 pg/mL) at admission. Abdominal CT and magnetic resonance imaging (MRI) revealed a hypervascular tumor of the pancreatic head (2×3 cm) and bilateral adrenal gland nodules. Although gastrinoma was suspected, a definite diagnosis could not be made because the serum gastrin level was only modestly increased. Regarding the patient's bilateral adrenal nodules, chemical-shift MRI showed the presence of lipid-containing adenomas. Although the baseline adrenal hormone levels were normal (Table 1), overnight dexamethasone suppression tests revealed that the cortisol level after 1 mg of dexamethasone was 4.2 μg/dL (Table 2), which was not significantly suppressed (8). In addition, her dehyroepiandro sterone sulfate (DHEA-S) level was low (Table 1), and she lacked the characteristic features of Cushing's syndrome. Based on these findings, the patient met the diagnostic criteria for subclinical adrenal Cushing's syndrome (8). Furthermore, her serum baseline value for prolactin (PRL) was 57.23 ng/mL (normal range: 6.12-30.54 ng/mL), and her response of PRL to thyrotropin-releasing hormone (TRH) was blunted (Table 2). In contrast, the response of the patient's thyroid-stimulating hormone (TSH) to TRH as well as adrenocorticotropic hormone (ACTH), cortisol to corticotropin-releasing hormone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) to gonadotropin-releasing hormone were within the normal range.

Brain MRI showed a nodular lesion in the left anterior pituitary gland (6×5 mm; Knosp grade 0). The patient had gone through menopause around 1 year ago at 50 years old, and she had no galactorrhea or headache. Since she was taking only lansoprazole and sucralfate, drug-induced hyperprolactinemia was unlikely (9). She had no other causes of hyperprolactinemia, including hypothyroidism and renal failure (Table 1) (9). The inadequate response of PRL to TRH stimulation supported the conclusion that the patient's pituitary tumor had caused hyperprolactinemia, although we were unable to eliminate the possibility of macroprolactinemia. Based on these findings, the patient was diagnosed

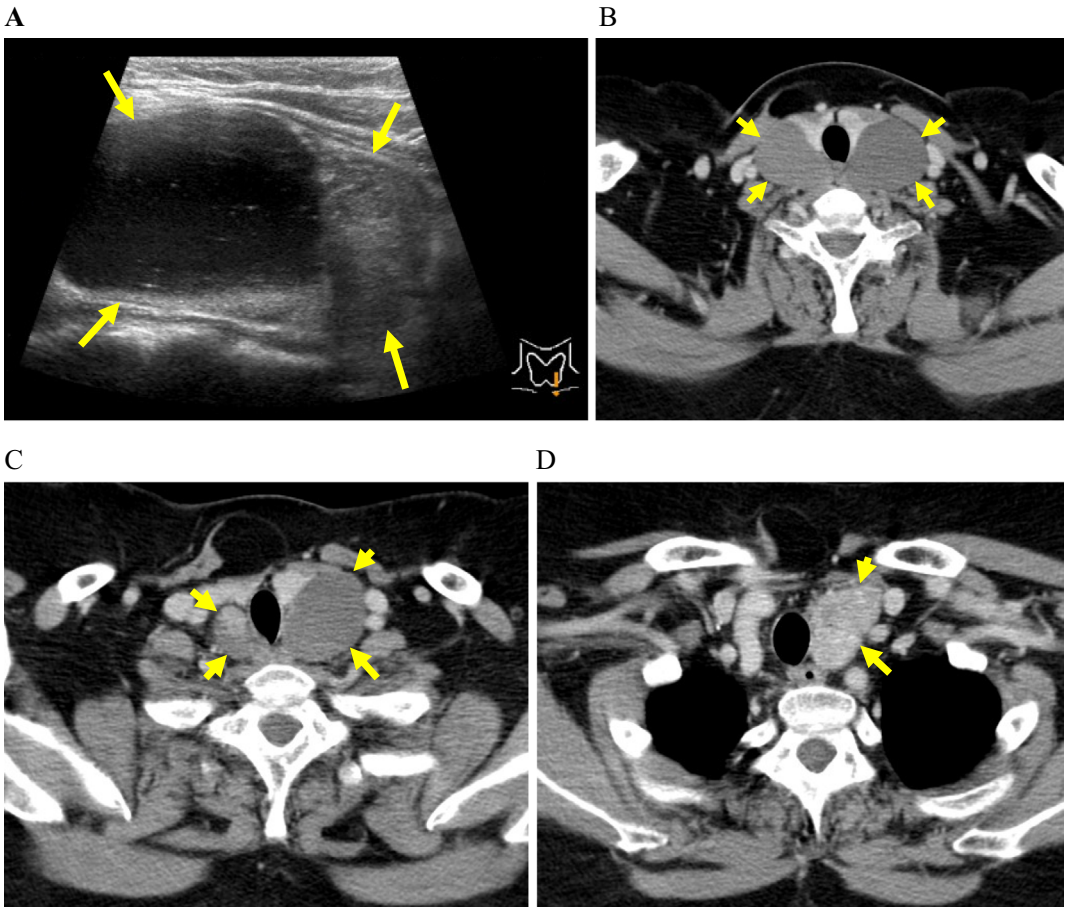

Figure 1. **(A) Ultrasonography showing a large cyst and a solid lesion at the lower part (arrows) of the left inferior portion of the thyroid gland. (B) Computed tomography (CT) showing large cysts at both sides (arrows). (C) CT showing a hypervascular solid lesion (right) and cyst (left). (D) CT showing a hypervascular solid lesion (left).**

with MEN1.

Regarding her family history, the patient's 74-year-old mother had a history of primary hyperparathyroidism and insulinoma. The patient and one of her first-degree relatives developed MEN1-associated tumors, suggesting familial MEN1. Following recommendations from a consensus statement and clinical practice guidelines for MEN1, the patient and her mother underwent genetic testing for *MEN1* after giving informed consent and receiving genetic counseling (2, 3). Germline DNA sequencing revealed that they both had a missense mutation (c.1013T>G, p.Leu338Pro) in exon 7 of *MEN1*. No mutations were identified in the patient's 2 sisters (45 and 49 years old) or son (20 years old), who all had normal calcium levels.

To treat her primary hyperparathyroidism, the patient underwent total parathyroidectomy with autotransplantation. The bilateral cysts were the upper parathyroid glands, and the bilateral lower parathyroid glands were identified and excised. Half of the lower glands were cut into small pieces, and nine pieces were grafted onto the left forearm. The intact PTH level in the cystic fluid aspirated from the right cyst during the operation was 1,170,000 pg/mL, whereas the fluid thyroglobulin level was low. Fluids were unable to be obtained from the left cyst. The pathological findings showed bilateral upper parathyroid glands macroscopically forming cysts (right, 5×2×1 cm; left, 6×2×2 cm) and solid lesions in the lower parts, which exhibited hyperplasia histologically.

For her pancreatic head tumors, the patient underwent surgical resection as a diagnostic and therapeutic approach. Her serum gastrin level was 104 pg/mL (normal range: 37-172 pg/mL) after parathyroidectomy. The tumor was diagnosed as a pancreatic neuroendocrine tumor (PanNET) grade 1 (G1) based on histopathological and immunohistochemical analyses. No findings suggested that the patient had gastrinoma as the primary cause of her high serum gastrin levels.

After these treatments, the patient was followed up in an ambulatory care setting. Each lesion was assessed routinely. Hyperparathyroidism was ameliorated because the serum levels of calcium and intact PTH were maintained within normal ranges. The patient demonstrated normal serum gastrin levels and no recurrence of PanNET on abdominal CT. Regarding the adrenal tumors, she had no Cushing's symptoms. The serum ACTH and cortisol levels were within the normal range, and abdominal CT showed that the tumors had not changed. For prolactinoma, no treatment was per-

formed, and the prolactin levels and MRI findings remained stable.

Discussion

We herein report a case of MEN1 with large parathyroid cysts harboring an uncommon missense mutation in the *MEN1* gene. In the patient's family, the mutation was cosegregated with MEN1-associated tumors. The proband had primary hyperparathyroidism, non-functioning PanNET, pituitary prolactinoma, and adrenal tumors. Furthermore, her mother with the same mutation had primary hyperparathyroidism and insulinoma. In contrast, three other family members with normocalcemia did not harbor this mutation. The same mutation in the MEN1 family has been previously reported in Sweden (10). In that family, the 37-year-old proband had primary hyperparathyroidism, a PanNET producing glucagon, insulin, pancreatic polypeptide, and gastrin, as well as pituitary prolactinoma. Two other family members of the Swedish patient had primary hyperparathyroidism and insulinoma, while another family member was presymptomatic. Insulinoma and prolactinoma highly affected these two families harboring the Leu338Pro mutation. Whether or not this mutation is associated with a tumor phenotype remains unknown. However, recent studies have suggested potential genotype-phenotype correlations in *MEN1* mutations (6). Thevenon et al. reported that the overall risk of death was higher when mutations including Leu338Pro affected the JunD interacting domain, a partner protein of MENIN (11). Thus, the mutation in our case might be associated with tumor phenotypes.

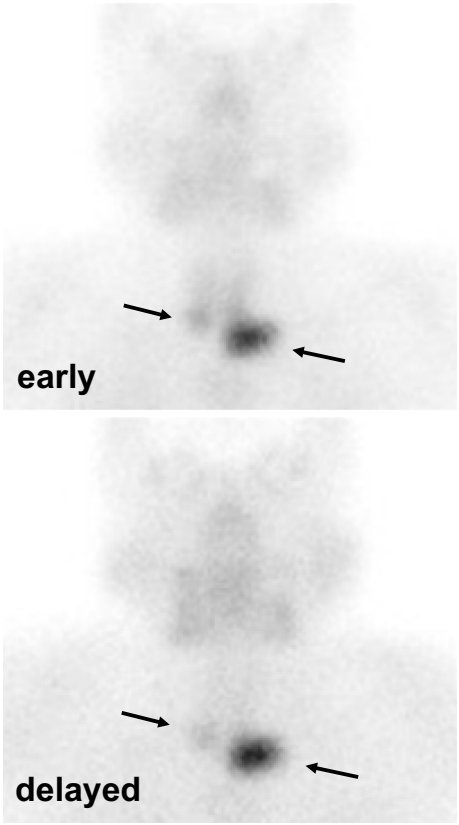

Figure 2. Technetium-99m-MIBI scintigraphy showing a high uptake (left predominantly) at the bilateral inferior portions of the thyroid gland in the early and delayed scans.

As a characteristic phenotype in our case, the patient had parathyroid cysts of the upper parathyroid glands on both sides. Parathyroid cysts are an uncommon disorder, accounting for only 1-5% of neck masses (12). Furthermore, functional cysts accounting for 10-15% of parathyroid cysts are a rare cause of primary hyperparathyroidism, with only 1-2% of patients having primary hyperparathyroidism (13-15). The cystic fluid of parathyroid cysts shows high PTH concentrations (12-14). Notably, the concentrations of PTH in functional parathyroid cysts can reach several million picograms per milliliter (13-16). In nonfunctional parathyroid cysts, cystic fluid PTH concentrations were not as high as those in functional cysts (13, 16). In the present case, the intact PTH level in the right cystic fluid was 1,170,000 pg/

Table 2. Endocrinological Examinations.

Dexamethasone suppression tests			
	Pre	1 mg	8 mg
ACTH, pg/mL	14	8	6
Cortisol, μg/dL	11.5	4.2	3.7

CRH (100 μg)+TRH (500 μg)+GnRH (100 μg) stimulation test					
	0 min	30 min	60 min	90 min	120 min
ACTH, pg/mL	25	98	48	25	19
Cortisol, μg/dL	9.8	35.9	33.1	25.3	25.3
TSH, μU/mL	0.18	6.49	4.24	2.62	1.87
Prolactin, ng/mL	42.82	48.33	45.10	42.31	42.03
LH, mIU/mL	11.97	95.51	113.76	99.09	80.98
FSH, mIU/mL	48.75	80.44	96.27	98.21	102.76

CRH: corticotropin-releasing hormone, TRH: thyrotropin-releasing hormone, GnRH: gonadotropin-releasing hormone

Table 3. Published Cases and the Present Case of Parathyroid Cysts in MEN1 Patients.

References	Age (y)	Sex	Calcium (mg/dL)	i-PTH (pg/mL)	Mutation of *MEN1*	Exon of mutation	No. pt. glands detected	No. pt. cysts	Location of pt. cysts	Pathology	Pituitary tumor	Pancreatic tumor	Other lesions
19	45	F	12	N/A	N/A		4	1	R-upper	Hyperplasia	+	+	
20	62	F	12.6	464	c.1659dupT	10	4	1	L-lower	Hyperplasia	+	+	Adrenal
17	46	M	11.8	112	c.1522C>T	10	4	4	All	Hyperplasia		+	
	30	F	11.3	85	c.613delT	10	3	1	R-lower	Hyperplasia		+	
	62	M	11.4	524	c.67ins5 bp	2	4	1	R-upper	Hyperplasia		+	
Present case	51	F	13.7	498	c.1013T>G	7	4	2	Bil-upper	Hyperplasia	+	+	Adrenal

F: female, M: male, i-PTH: intact PTH, N/A: not available, no: number, pt: parathyroid, R: right, L: left, Bil: bilateral, Adrenal: adrenal tumor

mL, which is compatible with a functional parathyroid cyst.

The parathyroid cysts in our case had distinctive clinicopathological features. However, the etiology contributing to the development of parathyroid cysts remains unclear. Previous reports suggest that nonfunctional parathyroid cysts may arise from vestigial remnants of the third or fourth branchial cleft or coalescence of microcysts (17, 18). For functional parathyroid cysts, a pre-existing parathyroid adenoma or carcinoma may cause cystic degeneration (16-18). In MEN1 cases, only five patients with parathyroid cysts have been previously reported (Table 3) (17, 19, 20). The types and exons of *MEN1* mutations varied. Since six patients, including our case with parathyroid cysts, had a pancreatic tumor, there may have been some time from the onset of the parathyroid cysts until their discovery (1, 2). All functional parathyroid cysts in MEN1 patients were shown to be histologically hyperplastic, suggesting that hyperplasia in MEN1 may cause cystic degeneration. Cavalli et al. reported that the incidence of functional parathyroid cysts was 4.2% in 71 patients with MEN1 (17). Given the lower incidence of functional parathyroid cysts in patients with primary hyperthyroidism (1-2%) than in MEN1 patients (14, 15), some genetic factors may be associated with the development of functional parathyroid cysts. Inactivating germline mutations of the *HRPT2* gene (also designated as *CDC73*) are related to hereditary hyperthyroidism-jaw tumor syndrome (HPT-JT) and a subset of familial isolated hyperparathyroidism (FIHP) (21, 22). Single or multiple parathyroid adenomas showing the most frequent manifestation in both diseases often present with cystic features (22). Because of the potential association between *HRPT2* mutations and the formation of cystic adenomas, *MEN1* mutations may contribute to the generation of functional parathyroid cysts through hyperplasia.

In summary, the present case was a MEN1 patient with large parathyroid cysts and a germline mutation in the *MEN1* gene. The coexistence of a rare clinical condition and a genetic variant identified in a single case demonstrates the phenotypic and genetic diversity of MEN1 syndrome.

The authors state that they have no Conflict of Interest (COI).

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