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<td>Murakami, Takaaki; Usui, Takeshi; Nakamoto, Yuji; Nakajima, Akio; Mochida, Yuki; Saito, Sumio; Shibayama, Takahiro; Yamazaki, Nobuhisa; Hatoko, Tomonobu; Kato, Tomoko; Yonemitsu, Shin; Muro, Seiji; Oki, Shogo</td>
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Challenging Differential Diagnosis of Hypergastrinemia and Hyperglucagonemia with Chronic Renal Failure: Report of a Case with Multiple Endocrine Neoplasia Type 1

Takaaki Murakami, Takeshi Usui, Yuji Nakamoto, Akio Nakajima, Yuki Mochida, Sumio Saito, Takahiro Shibayama, Nobuhisa Yamazaki, Tomonobu Hatoko, Tomoko Kato, Shin Yonemitsu, Seiji Muro and Shogo Oki

Abstract

A 53-year-old woman developed end-stage renal failure during a 15-year clinical course of primary hyperparathyroidism and was referred to our hospital for evaluation of suspected multiple endocrine neoplasia type 1 (MEN1). Genetic testing revealed a novel deletion mutation at codon 467 in exon 10 of the \textit{MEN1} gene. Systemic and selective arterial calcium injection (SACI) testing revealed hyperglucagonemia and hypergastrinemia with positive gastrin responses. A pathological examination revealed glucagonoma and a lymph node gastrinoma. The findings in this case indicate the importance of early diagnosis of MEN1 and demonstrate the utility of systemic and SACI testing in renal failure cases.

Key words: MEN1, glucagonoma, renal failure, calcium test, gastrinoma, AIMAH

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Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder which appears to be associated with heterozygous germinal mutations of the \textit{MEN1} tumor suppressor gene. MEN1 is clinically diagnosed by confirming the presence of neoplastic disease in at least two of the commonly affected organs: the parathyroid gland, endocrine pancreas, and anterior pituitary gland. The clinical presentation of MEN1 varies among individuals, with less common lesions including adenomas of the adrenal glands and neuroendocrine tumors (1, 2). However, previous studies have reported a substantial delay in the diagnosis of MEN1, and late diagnosis remains a clinical issue (3, 4).

The diagnosis of gastroenteropancreatic neuroendocrine tumors (GEPNETs), including gastrinomas and glucagonomas, remains challenging, which often leads to a delayed diagnosis in clinical settings (5). The measurement of plasma glucagon and serum gastrin levels has proven useful in the diagnosis of GEPNETs (6, 7), but it can be affected by various factors such as the renal function (7, 8). The clinical interpretation of hypergastrinemia and/or hyperglucagonemia in patients with both GEPNETs and renal impairment has yet to be fully elucidated and remains clinically challenging. Therefore, the impact of renal failure on the accuracy of GEPNET diagnosis remains unclear.

We herein report a case of a patient with MEN1 who presented with hypergastrinemia and hyperglucagonemia. We further describe the findings on endocrine evaluation under the conditions of renal failure, likely due to a 15-year history of primary hyperparathyroidism. The findings in the present case demonstrate the importance of early diagnosis of MEN1 and the clinical utility of systemic calcium infu-
A 53-year-old woman was referred to our hospital for evaluation of primary hyperparathyroidism and suspected MEN1. Primary hyperparathyroidism had developed at age 38, for which she underwent 3 separate parathyroidectomies of the bilateral inferior glands and left superior gland over a 12-year period at another hospital. However, her intact parathyroid hormone (PTH) levels had not normalized. She developed recurrent nephrolithiasis, and consequently, her renal function declined. She began renal dialysis at the age of 50 years and was followed-up at a hemodialysis clinic. Her mother had presented with recurrent primary hyperparathyroidism, non-functional pancreatic neuroendocrine tumors, and a left adrenocortical tumor leading to a diagnosis of MEN1 at our hospital, with genomic DNA polymerase chain reaction (PCR) testing demonstrating a deletion mutation (c.1400delC) at codon 467 in exon 10 of the MEN1 gene. The patient’s current medications included furosemide (20 mg/day), 1α-hydroxyvitamin D3 (0.25 μg/day), mosaprid citrate hydrate (10 mg/day), precipitated calcium carbonate (1,000 mg/day), lanthanum carbonate hydrate (500 mg/day), and rebamipide (300 mg/day). The patient was 156.4 cm tall and weighed 61.2 kg. Her body mass index (BMI) was 25.0 kg/m². The patient did not complain of weight loss, diarrhea, black stool, erythema, or tetany. A physical examination revealed galactorrhea and the absence of a Cushingoid appearance. The findings on laboratory testing revealed normocalcemia (corrected serum calcium level, 9.4 mg/dL) with an elevated serum intact PTH level of 1,080 pg/mL measured using an electrochemiluminescence immunoassay (Mitsubishi Chemicals, Tokyo, Japan). 99mTc-technetium-sestamibi (99mTc-MIBI) scintigraphy revealed significant uptake in the right superior parathyroid gland and an anterior mediastinal tumor (shown with an arrow). The patient’s family history was otherwise unremarkable. Her brother died of a thymic neoplasm at 44 years of age; however, no detailed clinical information regarding this case was available. The patient’s family history was otherwise unremarkable.

Figure 1. (a) 99m technetium-sestamibi (99mTc-MIBI) scintigraphy demonstrating significant uptake in the right superior parathyroid gland and an anterior mediastinal tumor (shown with an arrow). (b) Cervicothoracic computed tomography (CT) and (c) T2-weighted magnetic resonance imaging (MRI) demonstrating a well-circumscribed tumor in the anterior mediastinum (shown with an arrow).

The patient’s family history was otherwise unremarkable. The patient’s family history was otherwise unremarkable. The patient’s family history was otherwise unremarkable. The patient’s family history was otherwise unremarkable. The patient’s family history was otherwise unremarkable. The patient’s family history was otherwise unremarkable. The patient’s family history was otherwise unremarkable. The patient’s family history was otherwise unremarkable. The patient’s family history was otherwise unremarkable. The patient’s family history was otherwise unremarkable. The patient’s family history was otherwise unremarkable. The patient’s family history was otherwise unremarkable. The patient’s family history was otherwise unremarkable.

Figure 2. Direct sequence analysis of the MEN1 gene. The sequencing analysis demonstrated a novel deletion mutation at codon 467 in exon 10.
The pancreas (SUVmax = 24.6; Fig. 3d). No evidence of duodenal uptake in this tumor in the distal region of the pancreas (SUVmax = 21.5) and a separate tumor in the body of the pancreas (3.21; Fig. 3c). DOTATOC-PET/CT similarly showed significant uptake in this tumor in the distal region of the pancreas. Diffusion-weighted imaging, as well as a significant uptake on 3T MRI (Fig. 3b) and a high signal intensity on abdominal CT and MRI revealed bilateral adrenocortical multiple nodules, with equivalent uptake on 131I-adosterol scintigraphy. The endocrine findings were consistent with a diagnosis of subclinical Cushing’s syndrome (Table 1).

In addition, abdominal dynamic CT revealed a ring-enhancing tumor in the distal region of the pancreas (Fig. 3a). The tumor showed a low signal intensity on T2-weighted MRI (Fig. 3b) and a high signal intensity on diffusion-weighted imaging, as well as a significant uptake on FDG-PET/CT (standardized uptake value [SUV]max = 3.21; Fig. 3c). DOTATOC-PET/CT similarly showed significant uptake in this tumor in the distal region of the pancreas (SUVmax = 21.5) and a separate tumor in the body of the pancreas (SUVmax = 24.6; Fig. 3d). No evidence of duodeenum, liver, or lymph node tumors were observed using any imaging modality, although upper gastrointestinal endoscopy revealed multiple erosions and raised submucosal nodules in the duodenum. The fasting blood samples had elevated levels of serum gastrin (550 pg/mL; normal range, 0-200 pg/mL) as measured by a radiolmmunoassay using the polyethylene glycol technique (SRL Inc., Tokyo, Japan) and plasma glucagon (1,310 pg/mL; normal range, 70-174 pg/mL) as measured using a double antibody radioimmunoassay (RIA; SRL Inc.), and decreased total plasma amino acid levels (1,864.8 nmol/mL; normal range, 2,068.2-3,510.3 nmol/mL) as measured via liquid chromatography-mass spectrometry (SRL Inc.). The results of a gastrin stimulation test after a calcium infusion were positive (serum gastrin: baseline, 560 pg/mL; 4 minutes after calcium infusion, 720 pg/mL), although the glucagon response was negative. Selective arterial calcium injection (SACI) testing was also performed, in accordance with previously reported methods (9, 10). A significant selective increase in gastrin from a baseline level of 640 pg/mL to a peak level of 2,000 pg/mL at 30 s after stimulation was observed in the gastroduodenal artery (GDA) but not in the superior mesenteric or splenic arteries. Endoscopic ultrasonography (EUS) revealed another tumor 13 mm in diameter while moving from the pancreatic head to the body. All three tumors were found to be gastrin-negative and glucagon-positive on an immunohistochemical analysis of the samples obtained from EUS-guided fine needle aspiration (EUS-FNA) cytology.

Because of the clinical possibility of gastrinoma, we performed total pancreatectomy with duodenum and right adrenal gland resection following mediastinal tumor resection. Although pancreaticoduodenectomy and enucleation of the tumors present in the body and tail of the pancreas were recommended in consideration of the patient’s quality of life, the patient and her family ultimately requested total pancreatectomy. After performing mediastinal tumor resection, the serum intact PTH level decreased to 512 pg/mL.
The findings on a pathological examination of the resected mediastinal tumor and right adrenal gland were consistent with ectopic parathyroid hyperplasia and macronodular adrenal hyperplasia, respectively. In addition, the pathological examination revealed numerous small tumors, measuring less than 5 mm in diameter, throughout the pancreas, but no duodenal tumors. A tumor 5 mm diameter was also observed in the pancreatic head in addition to the tumors detected preoperatively (Fig. 4a).

Concerning the tumor in the pancreatic head (Fig. 4b), immunochemical studies demonstrated positive staining for chromogranin A (Fig. 4c) and diffuse positive staining for glucagon (Fig. 4d). Concerning the tumors in the body and distal pancreas (Fig. 4f), the microscopic findings were consistent with neuroendocrine tumors, and immunochemical studies demonstrated spotty positive staining for glucagon (Fig. 4g). Therefore, these tumors were pathologically confirmed as glucagonomas. While the immunochemical studies showed that none of the pancreatic tumors expressed gastrin (Fig. 4e and h), a neuroendocrine tumor observed in the peripancreatic lymph node (Fig. 4i) was found to be positive for gastrin in an immunohistochemical analysis (Fig. 4j and k).

The Ki-67 proliferative indices of all tumors were less than 1%. The patient’s pathological staging was determined as T1bN1M0 (stage III) and T2N1M0 (stage III b), according to the AJCC/UICC and European neuroendocrine tumor society tumor node metastasis (TNM) staging system, respectively. After surgery, the plasma glucagon and serum gastrin concentrations decreased (Table 2), and the results of gastrin stimulation testing after calcium infusion were negative (serum gastrin: baseline, 26 pg/mL; 4 minutes after calcium infusion, 80 pg/mL).

**Discussion**

We herein report the case of a patient who was clinically diagnosed with MEN1 due to the presence of primary hyperparathyroidism, pancreatic NETs (pNETs), and a prolactinoma. The patient was also found to have hypergastrinemia and hyperglucagonemia with end-stage renal failure as a result of a 15-year history of primary hyperparathyroidism. Although the renal function is known to affect serum levels of gastrin and plasma glucagon, a gastrinoma of the...
peripancreatic lymph node and pancreatic glucagonomas were revealed by pathological examinations. Few reports have so far been published regarding MEN1 in patients with renal failure, and endocrine evaluations of GEPNETs are also rarely described (11).

MEN1 germline mutation testing has demonstrated substantial utility in the diagnosis of MEN1 and should be offered to index patients with MEN1 and their relatives (1, 2). Heterozygous germline mutations of the MEN1 gene have been identified in approximately 90% of all MEN1 patients. In the present study, a direct sequence analysis revealed a deletion mutation at codon 467 in exon 10 of the MEN1 gene. To our knowledge, this mutation has not been previously reported (12) or registered in the Human Gene Mutation Database (HGMD®).

Our case demonstrated the importance of early diagnosis of MEN1. The diagnosis of MEN1 is often delayed (3, 4), as was the case in the present patient in whom the interval between the diagnosis of early-onset primary hyperparathyroidism with multiglandular hyperplasia and that of MEN1 was 15 years. During this interval, she developed end-stage renal failure that was most likely due to recurrent primary hyperparathyroidism. A previous study reported that urolithiasis-related renal complications in MEN1-associated primary hyperparathyroidism were more frequent and progressive than sporadic complications (13). Supernumerary and/or ectopic parathyroid glands are common in MEN1 cases, as observed in the present case (14). In addition, total parathyroidectomy with autotransplantation or subtotal parathyroidectomy should be recommended in MEN1 cases (1). The characteristic symptoms of MEN1 should not be overlooked, and its diagnosis should always be considered as a differential diagnosis due to the potential effects of MEN1 on the renal function and its implications for diagnostic and therapeutic strategies for primary hyperparathyroidism. As a final note, residual parathyroidectomy should be considered in the present case in the near future.

Endocrine evaluation of pNETs is clinically important. As previously reported, more than one type of functional pNET (e.g. gastrinoma and glucagonoma) may be observed in patients with MEN1, as in the present case (15). Hypergastrinemia in patients with renal failure is a well-known clini-
either the traditional RIA or a sandwich ELISA has substan-
tial utility in the diagnosis of glucagonoma, even in patients
with renal failure. However, we were unable to clarify the
superiority of the traditional RIA or the sandwich ELISA
for measuring the plasma glucagon level in the present
study, since a direct comparison between these two assays in
renal failure cases has not been validated.

Regarding the relationship between bilateral macronodular
adrenal hyperplasia and MEN1, adrenal cortical tumors are
recognized in almost 40% of MEN1 patients (1, 2). Al-
though bilateral macronodular adrenal hyperplasia including
ACTH-independent macronodular adrenal hyperplasia (AI-
MAH) is rare in MEN1 cases (23), a previous report
showed that pNETs were present in all of the the MEN1 pa-
ients with adrenal involvements (24). The present case
might also suggest a close relationship between the develop-
ment of pNETs and adrenal lesions in MEN1 (23).

In summary, we herein reported a case of MEN1 with a
novel deletion mutation at codon 467 of the
MEN1 gene. Hyperglucagonemia and hypergastrinemia with renal failure
were observed in the present case, in addition to positive
gastrin responses on systemic calcium infusion and SACI
testing. A pathological examination demonstrated the pres-
ence of multiple glucagonomas and a lymph node gastrin-
oma. The findings in the present case highlight the impor-
tance of the early diagnosis of MEN1 and the utility of sys-
temic calcium infusion and SACI testing in diagnosing gas-
trinoma, even in patients with renal failure.

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

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Table 2. Laboratory Results before and after the Pancre-

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<tr>
<td>Glucagon (pg/mL)</td>
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<td>-</td>
<td>9.2-44.8</td>
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RIA: radioimmunoassay, ELISA: enzyme-linked immunosorbent assay
Glucagon RIA and sandwich ELISA measured by SRL Inc., Tokyo, Japan.

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